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HEPATIC COMA*

A Clinical, Laboratory and Pathological Study

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PHILADELPHIA

COMA is a terminal event frequently observed in patients with hepatic disease. This state is first characterized by lethargy or abnormal excitement and progresses to unconsciousness, often attended by convulsions, in the immediate period before death. The convulsions are most often focal but a localized brain lesion is seldom demonstrated at autopsy to explain them. The appearance of the disordered mental state, the convulsive episodes and the coma coincides with what appears to be serious metabolic decompensation. Fever, fetor hepaticus, deep "blowing-off" respirations, dryness of mucous membranes, muscular twitchings, oliguria and anuria are some of the findings suggestive of gross physiologic breakdown.

Hepatic coma may be the result of a number of processes affecting the liver. Hepatitis, cirrhosis and cancer, with invasion of the liver, are among the possible causes.[1-3] Although hepatic parenchymal failure with coma may occur suddenly without apparent provocation, it more often follows the impact of such factors as infection, hemorrhage, overzealous paracentesis, sedation or surgical procedures.

Little is known concerning the deranged mechanisms producing hepatic coma.[4] Comparison of routine hepatic tests in the precoma and coma periods fails to reveal any marked difference to explain the change in physical state.[2, 5] It is unlikely that a single factor or group of factors will be discovered. The plurality of liver function should at the start discredit the proposal of a single mechanism.

A review of the medical literature reveals a very limited investigation of this subject. At the Philadelphia General Hospital, a large number of patients with advanced liver disease were available for study. During the one-year period of the study, 11 consecutive cases satisfied the requirements for the diagnosis of hepatic coma. These requirements consisted of the presence of lethargy or unconsciousness, fetor hepaticus, jaundice, spider angiomas, hepatomegaly and ascites. All the presumptive evidence for chronic liver disease was substantiated by findings at autopsy.

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METHODS

When a patient was admitted in hepatic coma, one or two members of the investigating group were called. An immediate evaluation of the history was made. Particular attention was given to history suggesting previous hepatitis, alcoholism or nutritional deficiency, or all three. The physical examination was completed, and the results were checked independently by another observer. After the original examination had been completed, the following blood studies were made at once: routine studies, including hemoglobin, white-cell and differential counts, hematocrit, blood sugar, blood urea nitrogen and blood Wassermann reaction; electrolyte studies, including carbon dioxide combining power, blood pH, serum chloride, serum sodium, serum potassium, serum calcium and serum phosphorus; liver-function tests, including serum bilirubin, cephalin-cholesterol flocculation, thymol turbidity, thymol flocculation, alkaline phosphatase and prothrombin time; and metabolic studies, including nonprotein nitrogen, blood uric acid, serum cholesterol, serum cholesterol esters, serum albumin, serum globulin, total fatty acids, phospholipids, blood pyruvic acid, blood lactic acid, blood ketones and alpha-keto-glutaric acid.

Whenever possible, all blood samples were drawn as soon as the patient was admitted and before any parenteral therapy had begun. In 1 case (Case 10) an infusion of glucose had been completed six hours before blood specimens had been taken.

The values for neutral fats and total blood lipids were calculated from the lipid determinations mentioned above. We determined the number of milligrams of phospholipids by multiplying the number of milligrams of lipid phosphorus and the factor 25.[6] The total fatty acids were converted from millimols per liter to milligrams per 100 cc. by multi-

plication with the factor 269.[7] The Bloor formula, which states that,"neutral fats equals total fatty acids minus 2/3 the sum of cholesterol esters and phospholipids," was used to calculate the neutral fats in milligrams per 100 cc.[8] This is not exact, for it fails to account for the three carbons of glycerol. However, this error is a small one. The total fats were estimated by the addition of the values of neutral fats, total cholesterol and phospholipids.

The gross and microscopical findings of autopsy were reviewed and listed.

No effort was made to evaluate the effectiveness of the various therapeutic regimens on the coma or the biochemical alterations that might have been incident to it. The treatment of these patients was under the control of the different medical services and invariably included the application of conventional measures.

Results

The physical findings are summarized in Table 1. Seven of the 11 patients were in coma when first seen. Three were mentally dull or stuporous. Only 1 could be described as hyperirritable. Icterus, spider angiomas, gynecomastia, liver palms and collateral abdominal venous collaterals were present in the usual frequency seen in patients with liver disease without hepatic coma.[9] Most patients had a slight elevation of temperature. The pulse rate, as well as the respiratory rate, was elevated in all cases. The respirations of these patients were deep, and characteristic in most cases of Kussmaul breathing. It is worthy of note that the blood pressures of most of these patients were at the lower limits of a normal range or even at shock levels. None of the patients with advanced hepatic insufficiency manifested hypertension. Bleeding in 8 of the patients might be offered as an explanation for hypotension. When overt bleeding had stopped there was improvement in the blood-pressure recording, but even in the absence of a bleeding tendency blood pressures remained in the low range. These bleeding tendencies were manifested by nasal hemorrhage, purpura and ecchymosis, hematemesis and melena. The recognition of hemorrhage preceded the onset of coma in all cases. The livers of 6 patients were enlarged on physical examination, and the depth of extension below the right costal margin was recorded in centimeters. In only 3 cases could the liver be designated as nonpalpable. The spleen was definitely enlarged on palpation in 2 and questionably enlarged in 2. This was an unexpectedly low number of palpable spleens in cases in which portal hypertension was invariably noted. The presence of ascites contributed to the difficulty of palpation. The altered physical state of coma made it impossible to obtain a forced deep inspiration in most patients. One or both of these factors

Table 1. *Summary of Physical Findings.*

Case No.	Age	Sex	Race	Mental Status	Icterus	Spider Nevi	Gynecomastia	Liver Palm	Collateral Venous Channels
	yr.								
1	61	M	W	Comatose	Present	Present	Present	Absent	Present
2	54	M	W	Comatose	Absent	Absent	Absent	Absent	Absent
3	71	M	W	Irritable	Present	Present	Absent	Present	Present
4	44	M	W	Comatose	Present	Present	Present	Absent	Present
5	48	M	W	Comatose	Present	Present	Present	Present	Present
6	56	M	W	Comatose	Present	Present	Absent	Present	Present
7	44	M	N	Dull	Present	Absent	Absent	Absent	Absent
8	48	F	N	Stuporous	Present	Absent	—	Absent	Absent
9	43	F	W	Comatose	Present	Present	—	Absent	Present
10	—	—	—	Comatose	Present	Present	Absent	Present	Present
11	54	M	W	Dull	Present	Present	Absent	Present	Present

Table 2. *Routine Blood Studies in Hepatic Coma.*

Case No.	Duration of Coma before Study	Hemoglobin	White-Cell Count	Neutrophils	Lymphocytes	Monocytes	Eosinophils	Basophils	Hematocrit	Blood Sugar	Blood Urea Nitrogen	Serologic Test for Syphilis
		mg./100 cc.	*×10³*	*%*	*%*	*%*	*%*	*%*	*vol. per cent*	*mg./100 cc.*	*mg./100 cc.*	
1	20¼ hr.	8.8	8.3	83	7	6	1	3	—	—	12	Negative
2	72 hr.	7.9	4.45	54	26	11	9	0	27	132	11	Negative
3	14 days	11.2	16.8	—	—	—	—	—	—	117	31	Negative
4	48 hr.	8.6	19.5	80	17	2	1	0	—	107	85	Negative
5	24 hr.	11.2	6.3	63	26	6	5	0	35.2	—	—	Negative
	72 hr.	—	—	—	—	—	—	—	—	222	13	
	7 days	13.0	24.7	—	—	—	—	—	38.8	84	14	
6	24 hr.	13.6	17.1	88	10	2	0	0	44.0	50	14	Negative
7	48 hr.	8.7	14.8	82	13	5	0	0	26.0	95	13	Negative
8	8 days	7.5	14.3	76	19	5	0	0	26.2	97	16	Negative
9	48 hr.	5.5	23.75	80	16	2	2	0	16.1			Negative
10	36 hr.	11.4	6.25	91	9	0	0	0	35.3	114*	7	Negative
11	4 days	11.9	18.35	—	—	—	—	—	38.3	104	28	Negative

*Glucose.

affected the physical findings so far as the size of spleen was concerned.

Table 2 presents a summary of the routine blood studies. All patients had significant decreases in chemical hemoglobin values. This finding correlated well with either the degree of hepatic parenchymal failure or the presence of bleeding. Decreases in the packed red-cell volume in 8 cases had similar explanations. Leukocytosis and an absolute increase in polymorphonuclear leukocytes are often observed in advanced hepatic disease when coma is imminent or present. Factors that determine this include hepatic cellular necrosis and infection in other areas. The blood sugar values, as determined by Somogyi's modification of the Folin–Wu method, were low with the highest level (Case 4), massive gastrointestinal hemorrhage was observed. As with normal blood sugar values, the presence of normal results for blood urea in most cases suggests preservation of another function in some cases of advanced parenchymal failure.

A summary of routine hepatic tests is recorded in Table 3. The serum bilirubin levels were elevated (normal 1 mg. per 100 cc.) in all cases. In some of these, the elevations were marked, as would be expected with severe parenchymal degeneration or infiltration. The uniformity of jaundice in cases of chronic liver disease, all terminating fatally, emphasizes the serious portent of this finding in patients with cirrhosis. There is nothing in the

Table 1 (*Concluded*).

Case No.	Temperature	Pulse	Respirations	Blood Pressure	Ascites	Bleeding	Splenomegaly	Liver Size
	°F.							cm.
1	99–100°	88–110	25–40	108/60	Present	Present	Absent	—
2	100	92	25	125/70	Present	Present	Absent	—
3	98.6–101	80–130	24–36	132/80	Absent	Absent	Present	17.5
4	99–100	96–120	25–30	85/70	Present	Present	Absent	22.5
5	99–100	90–110	24–30	90/60	Present	Present	?	22.0
6	98°	130	60	0/0?	Present	Present	Absent	?
7	98–101	100	26	120/90	Present	Absent	Absent	15.0
8	102	104	20	84/58	Present	Absent	Absent	15.0
9	97	100	28	90/50	Absent	Present	Present	25.0
10	100	120	16	110/70	Present	Present	?	10.0
11	99	100	20	—	Present	Present	Absent	10.0

in only 2 of the patients studied. One (Case 5) had a random blood sugar of 222 mg. per 100 cc.; no history of diabetes could be elicited, and parenteral glucose therapy had not recently been given. These values are significant when considered with reports of low blood sugar levels in hepatic coma. The finding of a low blood sugar in a patient with advanced hepatic disease is significant and frequently explains disturbances in sensorium.[10] However, the entire physical derangement, with or without convulsive seizures, can occur in the presence of normoglycemia or hyperglycemia. The blood urea nitrogen was low in 1 case (Case 10) and elevated in 3 (Cases 3, 4 and 11). In the case

Table 3. *Routine Liver-Function Studies in Hepatic Coma.*

Case No.	Duration of Coma before Study	Serum Bilirubin	Total Protein	Serum Albumin	Serum Globulin	Cephalin Flocculation	Thymol Flocculation	Thymol Turbidity	Alkaline Phosphatase	Prothrombin Time
		mg./100 cc.	gm./100 cc.	gm./100 cc.	gm./100 cc.			units	Bodansky units	%
1	20½ hr.	7.18	6.9	1.1	5.8	++++	++	3.7	3.28	22
2	72 hr.	1.85	5.3	2.8	2.5	+	0	1.1	1.41	
3	14 days	4.44	6.0	3.3	2.7	0	+	1.5	18.95	37
4	48 hr.	30.0	6.0	3.2	2.8	++++	0	1.9	1.51	22
5	24 hr.	12.1	7.6	2.5	5.1	++++	0	4.8	3.50	12
	72 hr.	13.8	6.4	2.3	4.1	—	—	—	—	—
	7 days	12.0	7.2	3.6	3.6	0	0	5.0	3.10	22
6	24 hr.	22.7	6.9	2.9	4.0	++++	++++	4.5	—	10
7	48 hr.	19.4	5.8	1.9	3.9	++++	0	2.5	3.49	34
8	8 days	9.3	5.7	1.9	3.8	++++	++	3.45	3.69	24
9	48 hr.	24.4	5.0	3.4	1.6	+++	0	2.0	2.73	42
10	36 hr.	1.85	6.8	—	—	+++	0	3.4	1.5	34
11	4 days	7.36	6.9	5.8	1.1	++++	++++	5.0	6.34	32

phosphatase was elevated in only 1 case (Case 3). This patient had carcinoma of the stomach, with diffuse nodular metastasis of the liver. The alkaline phosphatase can be elevated in cases of metastatic carcinoma of the liver even when jaundice is not present.[12] However, it is not uncommon to find

protein level or partition that would separate these cases from those in which the outcome is more favorable. The cephalin-cholesterol flocculation was generally positive (24-hour reading) in comparison with the thymol test, which was usually negative until the eighteen-hour flocculation was recorded. This is the usual result in the majority of cases of Laënnec's cirrhosis.[11] The alkaline

elevations within the range marked in this case in cirrhosis without jaundice or evidence of intrahepatic obstruction. Prothrombin concentration is dependent on factors other than hepatic. However, the marked decrease noted in all cases undoubtedly reflects the degree of parenchymal failure. Unresponsiveness to parenteral administration of dioxide combining power was significantly lowered. Since the pH determinations were close to normal it could be assumed that these patients were in a state of compensated metabolic acidosis. We have no explanation for the low pH in Case 6. This patient was studied early when he had been in coma for less than twenty-four hours. It is possible that

TABLE 4. *Blood Electrolyte Studies in Hepatic Coma.*

CASE NO.	DURATION OF COMA BEFORE STUDY	SERUM SODIUM	SERUM POTASSIUM	TOTAL SERUM CALCIUM	SERUM PHOSPHORUS	BLOOD CHLORIDES	CARBON DIOXIDE COMBINING POWER	BLOOD pH
		milliequiv./liter	*milliequiv./liter*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*vol. per cent*	
1	20½ hr.	144	4.0	8.2	2.06	544	43	—
2	72 hr.	136	4.1	9.6	2.82	544	25	—
3	14 days	131	4.7	8.8	4.13	480	29	—
4	48 hr.	131	4.6	8.0	5.81	514	24	—
5	24 hr.	141	3.4	8.2	3.02	597	38	7.46
	72 hr.	147	3.5	—	—	556	37	7.59
	7 days	132	3.8	8.2	2.70	574	34	7.34
6	24 hr.	148	3.0	10.1	—	526	33	7.09
7	48 hr.	134	3.7	8.0	2.49	550	42	7.55
8	8 days	135	3.9	8.2	2.20	438	56	7.44
9	48 hr.	127	4.2	7.44	8.12	467	24	7.38
10	36 hr.	147	4.0	8.46	3.28	562	46	—
11	4 days	133	4.9	8.80	4.76	486	33	7.45

vitamin K in most cases points up the value of this determination as a prognostic index.

The electrolyte changes are summarized in Table 4.[13] Nine cases showed a slight decrease in the level of potassium below a normal of 4.2 milliequiv. per liter. This may have represented depletion due to starvation, vomiting or diarrhea. It was not possible in any of these cases to separate signs of hypokalemia from those of the general physical sufficient time had not elapsed for metabolic compensation.

A summary of carbohydrate, fat and protein metabolites is presented in Table 5. Blood nonprotein nitrogen, uric acid and urea nitrogen estimations represent a rough index of protein metabolism.

Blood lipid levels are also presented in Figure 1. We call attention to the markedly decreased choles-

TABLE 5. *Blood Studies of Protein, Fat and Carbohydrate Metabolites in Hepatic Coma.*

CASE NO.	DURATION OF COMA BEFORE STUDY	NON-PROTEIN NITROGEN	URIC ACID	TOTAL FAT	NEUTRAL FATS*	TOTAL FATTY ACIDS	PHOSPHO-LIPIDS	CHOLESTEROL		PYRUVIC ACID†	LACTIC ACID‡	ALPHA KETO-GLUTARIC ACID§	TOTAL KETONES¶
								TOTAL	ESTERS				
		mg./100 cc.	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*
1	20½ hr.	—	2.9	415.8	138.8	239.4	100.0	177.0	51.0	—	—	—	—
2	72 hr.	—	—	—	—	—	—	127.0	54.0	—	—	—	—
3	14 days	74	9.2	838.1	332.6	564.9	297.5	208.0	51.0	—	—	—	—
4	48 hr.	—	—	514.2	155.2	427.7	225.0	134.0	7.8	3.79	16.13	1.13	10.12
5	24 hr.	60	—	—	—	—	175.5	—	—	3.0	15.1	—	4.52
	72 hr.	—	—	—	—	—	163.0	—	—	—	—	—	—
	7 days	32	—	641.5	352.0	485.0	187.5	102.0	27.0	2.63	21.1	—	4.05
6	24 hr.	—	—	1587.6	1438.1	1506.4	84.5	65.0	17.0	4.04	65.2	—	5.09
7	48 hr.	24	3.78	—	—	—	286.25	127.0	33.0	3.51	20.8	—	—
8	8 days	24	—	917.79	799.89	863.49	67.79	50.2	27.6	5.33	49.8	—	—
9	48 hr.	164	13.35	441.1	249.1	328.1	113.0	79.0	5.9	3.45	32.5	—	—
10	36 hr.	15	2.70	280.68	187.18	247.48	61.50	32.0	29.0	2.52	18.3	—	—
11	4 days	18	—	326.52	58.77	223.27	215.75	52.0	31.0	5.45	19.5	—	—

*Calculated by the Bloor formula.
†Normal value 1.0 mg. per 100 cc.
‡Normal value 10.0 mg. per 100 cc.
§Normal value 0.6 mg. per 100 cc.
¶Normal value 1.5 mg. per 100 cc.

breakdown. Serum calcium was low in 9 cases. When these changes are correlated with those in the serum protein fractions it is noted that they could be explained by a decrease in the protein-bound calcium. In all cases except Case 5 the carbon terol esters in all cases studied.[5, 14] Interesting also is the lack or correlation between changes in cholesterol esters and serum phospholipids. For the most part, the neutral fat fraction was increased — markedly so in Case 6.

Pyruvic acid determinations were made in 8 of the 11 cases (Fig. 2). In all these cases the pyruvic acid levels were elevated above the normal of 1 mg. per 100 cc.

Lactic acid determinations are presented in Figure 3. In all cases in which this determination was done the values were elevated above a normal of 10 mg. per 100 cc.

Table 6 summarizes the autopsy findings in all cases. The increased liver weights are deserving of special notice. The microscopical findings constitute further proof that the underlying liver disease resulting in hepatic coma is not specific. The increased weight of the spleen in most of the cases recorded confirms the well known disparity between a palpable spleen and an enlarged spleen.

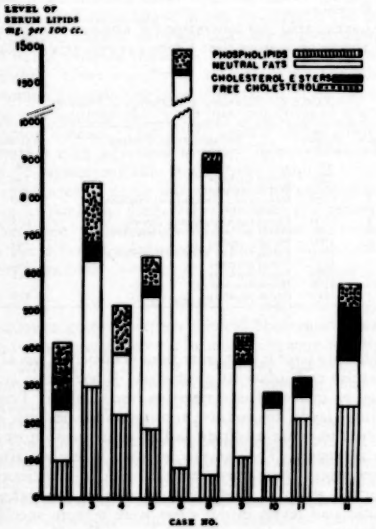

FIGURE 1. *Levels of Serum Lipids in Cases of Hepatic Coma.*

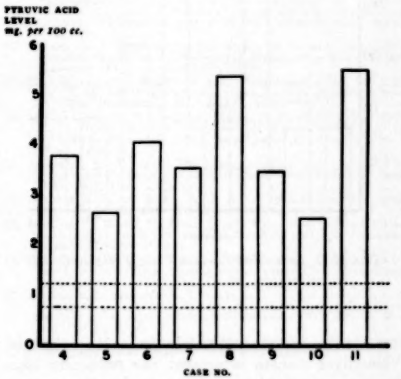

FIGURE 2. *Pyruvic Acid Levels in Cases of Hepatic Coma.*

DISCUSSION

These observations, for the most part, do not require further discussion. Some of the results are commented on.

Review of routine blood and hepatic tests serves to emphasize their lack of sensitivity for predicting or measuring hepatic coma. The maintenance of a normal blood sugar or blood urea nitrogen in most of these cases does not detract from the significance of a reduced level in the individual case with advanced parenchymal failure. The point can be made, however, that the physical derangements of hepatic coma do not necessarily depend on or coincide with depression of these levels. The serious implications of hyperbilirubinemia have already been stressed. In our experience with these and other cases of chronic liver disease, the appearance of jaundice marks the stage of serious parenchymal failure. The positive cephalin-cholesterol flocculations in most of the cases contrasts with the relative normalcy of the thymol-turbidity measurement. Two patients showed a negative cephalin-cholesterol flocculation; this is not an unusual finding in overwhelming or terminal hepatic disease. The alkaline phosphatase levels were normal or low except in 1 case with nodular metastasis. This finding in the presence of hyperbilirubinemia could best be explained on impaired regenerative activity of cholangiolar cells.

The blood electrolyte studies revealed little that could be ascribed to hepatic parenchymal failure. Electrolyte depression, when present, could be explained by inanition, vomiting, intubation losses or diarrhea. As stated above, calcium levels usually followed the levels of serum protein fractions.

The most significant findings in the lipid structure were decreases in cholesterol and cholesterol esters, and in phospholipids. Neutral fat and fatty acid levels showed no such consistent change. The results of these lipid measurements were either elevated, normal or low. There was lack of correlation in the levels of cholesterol esters and phospholipids, although both of these moved in the same general direction. Three of the serums studied had a decreased ratio of phospholipid to total lipid, and

yet none of these showed lipemic serum. It has been stated that the presence or absence of lipemic serum depends on the maintenance of a normal ratio of phospholipid to total lipid.[14-16]

Blood pyruvate may be elevated in many related or unrelated conditions, including starvation, nutritional deficiency, especially thiamine deficiency, periods of fever, physical exercise and large infusions of glucose.[17] In malnutrition without gross evidence of liver disease, the increased pyruvic acid in the

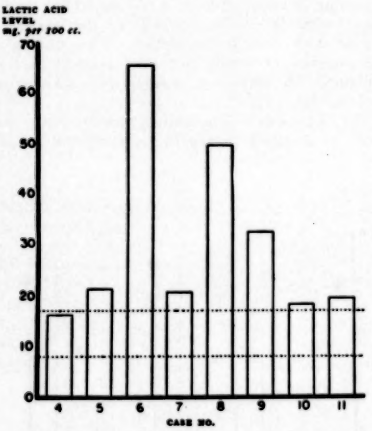

FIGURE 3. *Lactic Acid Levels in Cases of Hepatic Coma.*

blood falls significantly after thiamine injection. When liver disease is present the reduction after thiamine injection is less marked. In all our cases, starvation, thiamine deficiency and even fever could have been factors.

We were cognizant of work previously reported on elevated blood pyruvate and spinal-fluid pyruvate in liver injury.[1, 9, 17] We began our own study on the assumption that one default in hepatic coma, contributing to the altered physical state, was a breakdown in intermediate carbohydrate metabolism. Failure of full utilization of carbohydrate probably occurred at the tricarboxylic cycle. The findings of elevated blood pyruvic acid, blood lactic acid and, in 1 case, alpha-ketoglutaric acid levels suggest this.

All the factors mentioned that could cause an increase in blood pyruvate discourage the premise that the cause is necessarily hepatogenic. However, a failure of enzyme systems within the fatty liver, the fibrotic liver or the infiltrated liver would probably impair the phosphorylation of thiamine. Phosphorylated thiamine is necessary for complete utilization of pyruvic acid. There is much to support the proposition that the biochemical disturbance in thiamine deficiency is an inability of the cell to metabolize pyruvic acid.[17] Further evaluation of the effect of nutritional deficiency without gross evidence of liver disease will be necessary to clarify the importance of this disturbance in hepatic coma and the value of the determination of blood pyruvate in predicting or measuring advanced hepatic insufficiency.

Lactic acid concentration is affected by many of the same factors that affect pyruvic acid, among

TABLE 6. *Summary of Pathological Findings.*

CASE NO.	WEIGHT OF LIVER	MICROSCOPICAL FINDING	WEIGHT OF SPLEEN
	gm.		gm.
1	1200	Portal cirrhosis	180
2	1300	Portal cirrhosis	350
3	6000	Metastatic squamous-cell carcinoma (stomach)	280
4	2900	Portal cirrhosis; hemosiderosis.	675
5	2600	Portal cirrhosis; fatty dystrophy.	230
6	1000	Portal cirrhosis	100
7	1930	Portal (?) and biliary (?) cirrhosis	250
8	1820	Portal cirrhosis	360
9	3090	Portal cirrhosis	411
10	1500	Hemochromatosis	
11	1840	Portal cirrhosis	170

which are liver injury, nutritional deficiency, anoxia, exercise and infusions of glucose. Blood lactic acid may be increased in congestive heart failure. Liver injury leads to lactate accumulation because of failure to convert lactate and its subsequent storage as glycogen. The lactate increase is higher after liver injury than after simple nutritional deficiency. For this reason it might be assumed that the highest lactic acid levels in our cases were a more specific reflection of serious liver injury. The factor of anoxia would have to be recognized but could not be measured.

In all our cases blood ketones were markedly increased. This could have resulted from inanition or starvation with preservation of an intact mechanism for the production of ketones.

Recently, resemblances between hepatic coma and ammonium intoxication have been reported.[18, 19] Ammonium is a intracellular cation that in excess can arrest normal nerve-cell function, causing lethargy, coma and death. One of the pathways for the removal of ammonium from the nerve cells depends upon the presence of physiologic amounts of glutamic acid. It is conceivable that an excess of other amino acids in the extracellular fluids as might occur in hepatic insufficiency interferes with this important role of a single amino acid.[20] The result would be intracellular ammonium intoxication.

In our cases, we were unable to obtain blood ammonium levels. We have since become convinced,

that the important determination of the role of this factor would depend on some direct or indirect measurement of intracellular ammonium. None of the patients received ammonium-containing cation-exchange resins. In other cases on our wards, observed before signs of lethargy have appeared, the application of such resin therapy has initialed toxic symptoms indistinguishable from those of early hepatic coma. Since the report of Gabuzda et al.[18, 19] none of our patients with liver disease have received resins containing an ammonium exchange.

A brief consideration of the autopsy data shows that most of these cases with terminal hepatic insufficiency had enlarged livers by weight. If one considers 1500 gm. to be about a normal liver weight all but 3 patients (Cases 1, 2 and 6) had increased weights. Liver atrophy at autopsy is not the most common gross finding in nutritional cirrhosis. There was no disagreement in the interpretation of microscopical tissues. This might appear to be unusual in cases with advanced hepatic disease. However, any disagreement that might have resulted if only a small area of tissue was available for examination was avoided by preparation of multiple sections. The basic pathology in hepatic coma is varied, as the different microscopical findings in our cases demonstrated.

Summary

Eleven cases in which clinical observations suggested advanced hepatic insufficiency were followed to autopsy. Extensive laboratory studies were done in all cases. In all cases autopsy findings of advanced hepatic disease confirmed the clinical impression of coma from hepatic causes.

The comparative results of routine blood studies, blood electrolyte studies, hepatic tests and studies reflecting carbohydrate, fat and protein metabolism are recorded. Particular reference is made to evidence suggesting failure of utilization of carbohydrate through the tricarboxylic acid cycle. The factor of ammonium intoxication and resemblances to hepatic coma is discussed briefly even though we were unable to obtain blood ammonium levels.

The findings at autopsy are summarized, and emphasis is placed on the increased weights of the livers examined and the varied etiologic factors.

References

1. Snell, A. N., and Butt, H. R. Hepatic coma: observations bearing on nature and treatment. *Tr. A. Am. Physicians* 56:321-329, 1941.
2. Murphy, T. L., Chalmers, T. C., Eckhardt, R. D., and Davidson, C. S. Hepatic coma: clinical and laboratory observations on forty patients. *New Eng. J. Med.* 239:605-612, 1948.
3. Amatuzio, D. S., and Nesbitt, S. Study of pyruvic acid in blood and spinal fluid of patients with liver disease with and without hepatic coma. *J. Clin. Investigation* 29:1486-1490, 1950.
4. Ricketts, W. E., Kirsner, J. B., and Palmer, W. L. Clinical observations on severity of liver failure in portal cirrhosis. *Gastroenterology* 15:245-256, 1950.
5. Ricketts, W. E., Kirsner, J. B., Kippen, D. D., and Palmer, W. L. Tests of "hepatic function" in portal cirrhosis. *Gastroenterology* 15:40-51, 1950.
6. Youngburg, G. E., and Youngburg, M. V. Phosphorus metabolism: system of blood phosphorus analysis. *J. Lab. & Clin. Med.* 16: 158-166, 1930.
7. Man, E. B., and Gildea, E. F. Modification of Stoddard and Drury titrimetric method for determination of fatty acids in blood serum. *J. Biol. Chem.* 99:63-69, 1932.
8. Bloor, W. R. *Biochemistry of the Fatty Acids and Their Compounds, the Lipids.* 387 pp. New York: Reinhold, 1943.
9. Bean, W. B. Cutaneous arterial spider: survey. *Medicine* 24:243-331, 1945.
10. Mellinkoff, S. M., and Tumulty, P. A. Hepatic hypoglycemia. *New Eng. J. Med.* 247:745-750, 1952.
11. Neefe, J. R., Bahnson, E. R., and Reinhold, J. G. Studies of responses of certain hepatic tests in diseases of liver and biliary tract. I. Serum cephalin cholesterol flocculation, thymol turbidity, thymol flocculation and colloidal gold responses. *Gastroenterology* 9:656-671, 1947.
12. Watson, C. J. Some biochemical studies of hepatitis with special reference to problem of differentiating medical and surgical jaundice. *Canadian M. A. J.* 61:483-489, 1949.
13. Eisenmenger, W. J., Blondheim, S. H., Bongiovanni, A. M., and Kunkel, H. G. Electrolyte studies on patients with cirrhosis of liver. *J. Clin. Investigation* 29:1491-1499, 1950.
14. Stueck, G. H., Jr., Rubin, S. H., Clarke, D. H., Graef, I., and Railli, E. P. Studies on patients with cirrhosis of liver: plasma and liver lipid distribution and its relation to pathology of liver. *Am. J. Med.* 8:188-201, 1948.
15. Ahrens, E. H., Jr. Lipid disturbance in biliary obstruction and its relationship to genesis of arteriosclerosis. *Bull. New York Acad. Med.* 26:151-162, 1950.
16. Carfagno, S. C., and Steiger, W. A. Serum lipids in lipemia retinalis. *Am. J. M. Sc.* 221:379-383, 1951.
17. Bueding, E., Wortis, H., Stern, M. and Esteronne, D. Pathological variations in blood and spinal fluid pyruvic acid. *J. Clin. Investigation* 21:85-89, 1942.
18. Gabuzda, G. J., Jr., Phillips, G. B., and Davidson, C. S. Reversible toxic manifestations in patients with cirrhosis of liver given cation-exchange resins. *New Eng. J. Med.* 246:124-130, 1952.
19. Phillips, G. B., Schwartz, R., Gabuzda, G. J., Jr., and Davidson, C. S. Syndrome of impending hepatic coma in patients with cirrhosis of liver given certain nitrogenous substances. *New Eng. J. Med.* 247:239-246, 1952.
20. Walshe, J. M. Observations on symptomatology and pathogenesis of hepatic coma. *Quart. J. Med.* 20:421-438, 1951.

yet none of these showed lipemic serum. It has been stated that the presence or absence of lipemic serum depends on the maintenance of a normal ratio of phospholipid to total lipid.[14-16]

Blood pyruvate may be elevated in many related or unrelated conditions, including starvation, nutritional deficiency, especially thiamine deficiency, periods of fever, physical exercise and large infusions of glucose.[17] In malnutrition without gross evidence of liver disease, the increased pyruvic acid in the

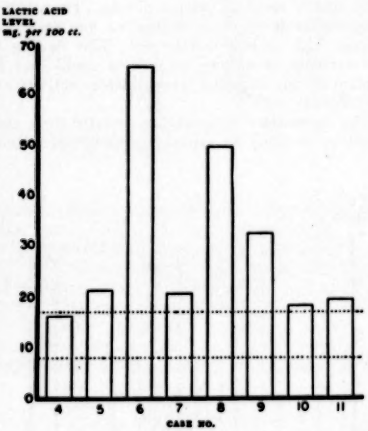

FIGURE 3. *Lactic Acid Levels in Cases of Hepatic Coma.*

blood falls significantly after thiamine injection. When liver disease is present the reduction after thiamine injection is less marked. In all our cases, starvation, thiamine deficiency and even fever could have been factors.

We were cognizant of work previously reported on elevated blood pyruvate and spinal-fluid pyruvate in liver injury.[1, 9, 17] We began our own study on the assumption that one default in hepatic coma, contributing to the altered physical state, was a breakdown in intermediate carbohydrate metabolism. Failure of full utilization of carbohydrate probably occurred at the tricarboxylic cycle. The findings of elevated blood pyruvic acid, blood lactic acid and, in 1 case, alpha-ketoglutaric acid levels suggest this.

All the factors mentioned that could cause an increase in blood pyruvate discourage the premise that the cause is necessarily hepatogenic. However, a failure of enzyme systems within the fatty liver, the fibrotic liver or the infiltrated liver would probably impair the phosphorylation of thiamine. Phosphorylated thiamine is necessary for complete utilization of pyruvic acid. There is much to support the proposition that the biochemical disturbance in thiamine deficiency is an inability of the cell to metabolize pyruvic acid.[17] Further evaluation of the effect of nutritional deficiency without gross evidence of liver disease will be necessary to clarify the importance of this disturbance in hepatic coma and the value of the determination of blood pyruvate in predicting or measuring advanced hepatic insufficiency.

Lactic acid concentration is affected by many of the same factors that affect pyruvic acid, among

TABLE 6. *Summary of Pathological Findings.*

CASE NO.	WEIGHT OF LIVER	MICROSCOPICAL FINDING	WEIGHT OF SPLEEN
	gm.		gm.
1	1200	Portal cirrhosis	180
2	1300	Portal cirrhosis	350
3	6000	Metastatic squamous-cell carcinoma (stomach)	280
4	2900	Portal cirrhosis; hemosiderosis.	675
5	2600	Portal cirrhosis; fatty dystrophy.	230
6	1000	Portal cirrhosis	100
7	1930	Portal (?) and biliary (?) cirrhosis	250
8	1820	Portal cirrhosis	360
9	3090	Portal cirrhosis	411
10	1500	Hemochromatosis	
11	1840	Portal cirrhosis	170

which are liver injury, nutritional deficiency, anoxia, exercise and infusions of glucose. Blood lactic acid may be increased in congestive heart failure. Liver injury leads to lactate accumulation because of failure to convert lactate and its subsequent storage as glycogen. The lactate increase is higher after liver injury than after simple nutritional deficiency. For this reason it might be assumed that the highest lactic acid levels in our cases were a more specific reflection of serious liver injury. The factor of anoxia would have to be recognized but could not be measured.

In all our cases blood ketones were markedly increased. This could have resulted from inanition or starvation with preservation of an intact mechanism for the production of ketones.

Recently, resemblances between hepatic coma and ammonium intoxication have been reported.[18, 19] Ammonium is a intracellular cation that in excess can arrest normal nerve-cell function, causing lethargy, coma and death. One of the pathways for the removal of ammonium from the nerve cells depends upon the presence of physiologic amounts of glutamic acid. It is conceivable that an excess of other amino acids in the extracellular fluids as might occur in hepatic insufficiency interferes with this important role of a single amino acid.[20] The result would be intracellular ammonium intoxication.

In our cases, we were unable to obtain blood ammonium levels. We have since become convinced,

that the important determination of the role of this factor would depend on some direct or indirect measurement of intracellular ammonium. None of the patients received ammonium-containing cation-exchange resins. In other cases on our wards, observed before signs of lethargy have appeared, the application of such resin therapy has initialed toxic symptoms indistinguishable from those of early hepatic coma. Since the report of Gabuzda et al.[18, 19] none of our patients with liver disease have received resins containing an ammonium exchange.

A brief consideration of the autopsy data shows that most of these cases with terminal hepatic insufficiency had enlarged livers by weight. If one considers 1500 gm. to be about a normal liver weight all but 3 patients (Cases 1, 2 and 6) had increased weights. Liver atrophy at autopsy is not the most common gross finding in nutritional cirrhosis. There was no disagreement in the interpretation of microscopical tissues. This might appear to be unusual in cases with advanced hepatic disease. However, any disagreement that might have resulted if only a small area of tissue was available for examination was avoided by preparation of multiple sections. The basic pathology in hepatic coma is varied, as the different microscopical findings in our cases demonstrated.

Summary

Eleven cases in which clinical observations suggested advanced hepatic insufficiency were followed to autopsy. Extensive laboratory studies were done in all cases. In all cases autopsy findings of advanced hepatic disease confirmed the clinical impression of coma from hepatic causes.

The comparative results of routine blood studies, blood electrolyte studies, hepatic tests and studies reflecting carbohydrate, fat and protein metabolism are recorded. Particular reference is made to evidence suggesting failure of utilization of carbohydrate through the tricarboxylic acid cycle. The factor of ammonium intoxication and resemblances to hepatic coma is discussed briefly even though we were unable to obtain blood ammonium levels.

The findings at autopsy are summarized, and emphasis is placed on the increased weights of the livers examined and the varied etiologic factors.

References

1. Snell, A. N., and Butt, H. R. Hepatic coma: observations bearing on nature and treatment. *Tr. A. Am. Physicians* 56:321-329, 1941.
2. Murphy, T. L., Chalmers, T. C., Eckhardt, R. D., and Davidson, C. S. Hepatic coma: clinical and laboratory observations on forty patients. *New Eng. J. Med.* 239:605-612, 1948.
3. Amatuzio, D. S., and Nesbitt, S. Study of pyruvic acid in blood and spinal fluid of patients with liver disease with and without hepatic coma. *J. Clin. Investigation* 29:1486-1490, 1950.
4. Ricketts, W. E., Kirsner, J. B., and Palmer, W. L. Clinical observations on severity of liver failure in portal cirrhosis. *Gastroenterology* 15:245-256, 1950.
5. Ricketts, W. E., Kirsner, J. B., Kippen, D. D., and Palmer, W. L. Tests of "hepatic function" in portal cirrhosis. *Gastroenterology* 15:40-51, 1950.
6. Youngburg, G. E., and Youngburg, M. V. Phosphorus metabolism: system of blood phosphorus analysis. *J. Lab. & Clin. Med.* 16: 158-166, 1930.
7. Man, E. B., and Gildea, E. F. Modification of Stoddard and Drury titrimetric method for determination of fatty acids in blood serum. *J. Biol. Chem.* 99:43-69, 1932.
8. Bloor, W. R. *Biochemistry of the Fatty Acids and Their Compounds, the Lipids.* 387 pp. New York: Reinhold, 1943.
9. Bean, W. B. Cutaneous arterial spider: survey. *Medicine* 24:243-331, 1945.
10. Mellinkoff, S. M., and Tumulty, P. A. Hepatic hypoglycemia. *New Eng. J. Med.* 247:745-750, 1952.
11. Neefe, J. R., Bahnson, E. R., and Reinhold, J. G. Studies of responses of certain hepatic tests in diseases of liver and biliary tract. I. Serum cephalin cholesterol flocculation, thymol turbidity, thymol flocculation and colloidal gold responses. *Gastroenterology* 9:656-671, 1947.
12. Watson, C. J. Some biochemical studies of hepatitis with special reference to problem of differentiating medical and surgical jaundice. *Canadian M. A. J.* 61:483-489, 1949.
13. Eisenmenger, W. J., Bloodheim, S. H., Bongiovanni, A. M., and Kunkel, H. G. Electrolyte studies on patients with cirrhosis of liver. *J. Clin. Investigation* 29:1491-1499, 1950.
14. Stueck, G. H., Jr., Rubin, S. H., Clarke, D. H., Graef, I., and Ralli, E. P. Studies on patients with cirrhosis of liver: plasma and liver lipid distribution and its relation to pathology of liver. *Am. J. Med.* 5:188-201, 1948.
15. Ahrens, E. H., Jr. Lipid disturbance in biliary obstruction and its relationship to genesis of arteriosclerosis. *Bull. New York Acad. Med.* 26:151-162, 1950.
16. Carfagno, S. C., and Steiger, W. A. Serum lipids in lipemia retinalis. *Am. J. M. Sc.* 221:379-383, 1951.
17. Bueding, E., Wortis, H., Stern, M. and Esterowne, D. Pathological variations in blood and spinal fluid pyruvic acid. *J. Clin. Investigation* 21:85-89, 1942.
18. Gabuzda, G. J., Jr., Phillips, G. B., and Davidson, C. S. Reversible toxic manifestations in patients with cirrhosis of liver given cation-exchange resins. *New Eng. J. Med.* 246:124-130, 1952.
19. Phillips, G. B., Schwartz, R., Gabuzda, G. J., Jr., and Davidson, C. S. Syndrome of impending hepatic coma in patients with cirrhosis of liver given certain nitrogenous substances. *New Eng. J. Med.* 247:239-246, 1952.
20. Walshe, J. M. Observations on symptomatology and pathogenesis of hepatic coma. *Quart. J. Med.* 20:421-438, 1951.

CARBOMYCIN THERAPY*

Results of a Brief Clinical Trial, Chiefly in Patients with Pneumonia

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AMONG the many active antimicrobial agents constantly emerging as a result of the various antibiotic and chemotherapeutic screening programs that are being carried out in many laboratories, few have reached the stage of active and extensive clinical trials. One of the most recent is erythromycin,¶ an antibiotic derived from a strain of *Streptomyces erythreus*.[1] This antibiotic was of particular interest because it was found to be highly active in vitro against gram-positive organisms, including various streptococci and staphylococci, of which increasing numbers of pathogenic strains now being isolated in many hospitals are found to be resistant to penicillin and to other antibiotics currently in wide use. In this hospital, a survey made at the time when erythromycin first became available for study indicated that strains of pathogenic staphylococci obtained from all sources were highly and quite uniformly sensitive to that agent irrespective of their sensitivity or resistance to any of the other available antibiotics.[2] The results of clinical and laboratory studies in this and other clinics have indicated that erythromycin may be useful in the treatment of gram-positive coccal infections, but that its usefulness may be limited in some patients with staphylococcal infections or with endocarditis by the rapid development of resistance of the infecting staphylococci and streptococci during the course of therapy.[3-5]

Meanwhile, carbomycin,‖ an antibiotic derived from a culture of *S. halstedii*, was discovered in another laboratory.[6] The preliminary announcement of this discovery indicated that carbomycin differed in some of its physical and chemical properties from erythromycin, which it resembled in being active primarily against gram-positive cocci and also against rickettsias and large viruses. It was also indicated that organisms acquire resistance to carbomycin in a step-wise fashion when transferred serially in the presence of that antibiotic.[6]

It was subsequently reported from the same laboratory that carbomycin is active in vitro against certain saprophytic mycobacteria, pleuropneumonia-like organisms and neisseria but not against fungi. Its activity was not appreciably altered by human or animal serum present in concentrations up to 20 per cent. It was found to be primarily bacteriostatic, but in larger concentrations bactericidal activity was apparent. The resistance pattern was described as comparable to that of penicillin, in contrast to the streptomycin pattern. No significant cross resistance was noted in vitro among carbomycin and penicillin, terramycin, aureomycin, chloramphenicol, polymyxin B, dihydrostreptomycin and bacitracin.[7] In high concentrations carbomycin was found to inhibit certain strains of protozoa, including *Endamoeba histolytica*, and to immobilize spermatozoa.[8] Carbomycin was capable of protecting mice against experimental infections with virulent streptococci, pneumococci and staphylococci, including 2 strains of the last that were resistant to other commercially available antibiotics.[9] Preliminary studies in rabbits indicated that significant peak levels could be obtained in plasma with large, single doses given intramuscularly or intravenously, but much lower levels were attained after similar oral doses. Variable concentrations were found in the urine of these rabbits, but only a small percentage of the total antibiotic administered could be recovered. The levels of carbomycin obtained in human plasma after single oral or intramuscular doses of from 3.3 to 18.0 mg. per kilogram of body weight did not exceed 0.625 microgm. per cubic centimeter.[10] The acute and chronic toxicity of carbomycin for laboratory animals was found to be of a low degree.[11]

Direct comparisons of the antibacterial action of carbomycin and erythromycin in vitro have been made in two laboratories.[12, 13] The results confirmed the fact that both agents are active against gram-positive cocci and neisseria and to a lesser extent against strains of hemophilus and clostridium but are essentially inactive against coliform and enteric bacilli. Against the great majority of sensitive strains, however, erythromycin was found to be appreciably and in many cases considerably more active, weight for weight, than carbomycin. This is clearly evident from the data obtained in both laboratories (Fig. 1). Moreover, it was shown in this laboratory,[13] that repeated subcultures of pathogenic strains of staphylococci and of certain streptococci in the presence of either erythromycin or carbomycin resulted in the development of strains

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¶Introduced by Lilly Laboratories under the trademark "Ilotycin."

‖Introduced by Charles Pfizer and Company, Incorporated, under the trademark "Magnamycin."

of increasing resistance to both agents. Cross resistance between the two antibiotics was practically complete.

Few clinical reports on the use of carbomycin are available at the time of this writing. One of these reports[14] deals with the treatment of 5 cases of staphylococcal infection with oral doses of 3 or 6 gm. daily. Clinical and bacteriological results were apparently favorable in 2 cases, but in 1 of these, an enterococcus was cultured from the wound throughout the period of therapy, although that organism was inhibited by 1.56 microgm. of carbomycin. In the other 3 cases the staphylococci were not eliminated by the therapy. In this report it is noted that the inhibitory concentrations of carbomycin for 25 strains of staphylococci, including those obtained from these 5 patients, ranged between 0.3 and 2.5 microgm. per cubic centimeter and for 25 strains of enterococci the range was between 0.156 and 2.5 microgm. However, even on daily doses of 3 or 6 gm., which produced disturbing gastrointestinal symptoms in 4 of the 5 patients, the serum concentrations ranged only from 0.04 to 0.32 microgm. per cubic centimeter.

In another clinical study[15] carbomycin was given to 15 patients with urinary-tract infections associated with gram-positive cocci; "clinical improvement, with bacteriologic sterility" resulted in 13 of these patients on oral doses of 2 gm. daily for a week. In addition, "a few patients with chronic urinary infection associated with noncorrectable uropathy were able to remain symptom free for long intervals on a maintenance dose of less than 1 gm. a day." Although data are not given, it was noted that there was good correlation between the laboratory findings and the actual response. However, blood and urine levels of carbomycin were extremely low and showed little or no correlation with clinical response; this observation was interpreted as indicating that such data are of questionable value since many patients responded favorably despite insignificant or even negative values.

At Wadsworth Hospital in Los Angeles[16] 57 patients with a variety of infections were treated with daily oral doses of 2 gm., except acutely ill patients, who were given 3 gm. daily by mouth for several days or 400 mg. intravenously every 6 or 8 hours for 24 to 96 hours. Good results were recorded in 34 of these patients and no effect in the remaining 23. In some of those with infections due to pneumococci, or to beta-hemolytic, alpha-hemolytic or nonhemolytic streptococci who responded favorably, the bacteriologic results were less striking than might have been expected from penicillin. The results in 5 patients with bacterial endocarditis were uniformly poor, and those in cases of staphylococcal sepsis were not striking. Good effects, however, were noted in 5 cases of amebiasis. Toxic effects included gastrointestinal symptoms in 10 patients and skin eruptions in 3, but these did not appear to be serious. In that study the activity of carbomycin against gram-positive cocci in vitro was confirmed, but the occurrence of relatively resistant strains of staphylococci was noted and resistance was readily produced in vitro. Also, whereas significant concentrations were achieved in plasma and urine after intravenous administration, the concentrations obtained after similar oral doses were quite low compared with the inhibiting concentrations for many of the organisms that are considered to be sensitive.

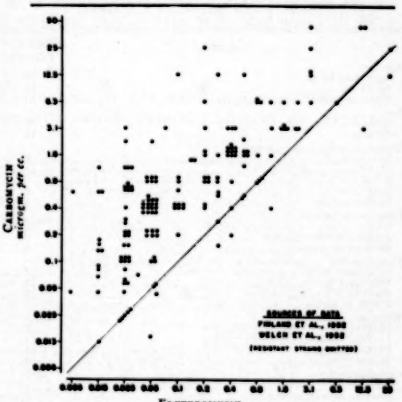

FIGURE 1. *Sensitivity of Bacterial Strains to Carbomycin and Erythromycin.*

A brief report is also available from Syracuse[17] on 20 patients with pneumococcal pneumonia; 12 of them were treated with erythromycin in an average daily dose of 1.5 gm. orally, and 8 received carbomycin in doses of 1.6 gm. orally or parenterally, or both. Clinical results were satisfactory in 9, and slow but complete resolution of pneumonia was observed in 5 others, 2 of whom showed pleural effusions during treatment. Three patients treated with erythromycin failed to respond satisfactorily; in 1 the clinical course was unaffected, and the sputum contained pneumococci for 72 hours, and in the other 2 empyema developed and both died. In 1 of the latter, sputum and blood cultures remained positive for 48 hours. There were also 3 failures on carbomycin therapy; pleural effusion and extension of pneumonia developed in 1 after 4 days of treatment. In another, blood cultures were positive after 24 hours, and an empyema developed 4 days later. The initial critical condition

of the third patient was unchanged for 48 hours, and her blood culture remained positive until penicillin was administered. No untoward side effects were observed from either drug, but the results were considered to be so unsatisfactory that extension of the study was precluded.

The present report deals with a limited clinical trial of carbomycin, chiefly in patients with pneumonia. In view of the results of preliminary laboratory studies, indicating that this antibiotic was appreciably less active than erythromycin against almost all the sensitive strains that were tested, and since plasma concentrations after oral administration of amounts approaching the maximum that could be tolerated were irregular, usually quite low and often not detectable, a deliberate attempt was made to avoid initiating treatment with carbomycin in patients who were critically ill. A total of 45 patients were treated between October, 1952, and April, 1953, all but 5 of them for pneumonia.

Table 1. *Observations in 40 Patients with Pneumonia at Time Treatment with Carbomycin Was Begun.*

Finding	No. of Patients
Age (years):	
Less than 40 yr.	12
40–59 yr.	16
60 yr. or over	12
Sex:	
Male	30
Female	10
Duration of acute symptoms:	
Less than 24 hr.	9
24–72 hr.	15
4–7 days	9
8–14 days	5
Indeterminate	2
Lung involvement:	
1 lobe	33
2 adjacent lobes (right)	6
Both lower lobes	1
Temperature:	
Less than 100°F.	2
100–101.9°F.	10
102–103.9°F.	21
104°F. or higher	7
White-cell count:	
10,000 or less	4
11,000–15,000	14
16,000–20,000	13
21,000 or more	9
Complications:	
Alcoholism	4
Cardiac failure, mild	1
Bronchiectasis	1
Result of sputum culture:	
Pneumococcus	31
Specific type 28	
Untyped 3	
Other organisms predominant	9
Hemophilus influenzae 1	
Alpha-hemolytic streptococcus 7	
Staphylococcus aureus 1	
Other organisms abundant (in sputums containing pneumococci)	10*
H. influenzae 6	
Beta-hemolytic streptococci 2	
Alpha-hemolytic streptococci 2	
Staph. aureus 2	
Klebsiella pneumoniae (atypical) 1	
Blood culture:	
Positive for pneumococcus	7
Negative	33
Estimated severity:	
Severe	2
Moderate	21
Mild	17

*2 organisms in each of 3 patients.

Results in Patients with Pneumonia

Selection of Cases for Carbomycin Therapy

An attempt was made to select patients who, at the time of admission to the hospital, had findings on history and physical examination that were characteristic of acute pneumonia and who denied having received any previous antibiotics or sulfonamides for this illness. Roentgenograms of the chest obtained en route to the ward, or shortly thereafter, confirmed the clinical findings in each case. Therapy with carbomycin was started promptly after symptomatic therapy had been instituted and after materials had been obtained for routine laboratory examinations, including blood and sputum for bacteriologic studies.

The relevant findings in these patients at the time therapy with carbomycin was started are summarized in Table 1. The patients were predominantly males under sixty years of age, who had a fairly brief acute illness, with temperature under 104°F., leukocyte counts below 20,000 and pulmonary involvement limited to a single lobe. The illness was judged, at the time, to be mild or of only moderate severity in all but 2 patients, both of whom appeared to be severely though not critically ill when the first dose of carbomycin was given. Underlying complicating conditions were infrequent and, except for mild congestive heart failure in 1 patient and severe acute alcoholism in 2 others, not disturbing.

Table 2. *Dosage of Carbomycin and Duration of Treatment.*

Datum	No. of Patients*
Oral administration:	
500 mg., then 250 mg. every 3 hr.	14 (1)
500 mg., then 250 mg. every 4 hr.	3
500 mg. every 4 hr.	21 (3)
500 mg. every 3 hr.	3† (1)
Intramuscular administration:	
400 mg. — single dose	1
400 mg., then 200 mg. every 3 hr. (total, 1.4 gm.)	1
Duration of treatment (oral)‡:	
2 days or less	3
3–4 days	8 (3)
5–7 days	15 (1)
8–10 days	9 (1)
11 days or more	3
Total oral dose§:	
Less than 5 gm.	3
6–10 gm.	7 (4)
11–15 gm.	8
16–20 gm.	13
20–30 gm.	7 (1)

*Patients other than those with pneumonia indicated in parenthesis.
†These 3 patients had previously received 250 mg. every 3 hr.
‡Average 5.7 days.
§Average 14.7 gm.

The causative organism in 31 cases was judged from sputum cultures to be a pneumococcus, 15 specific types being identified in 28 of these patients. Blood cultures were positive for pneumo-

cocci in 7 patients — Types 1, 2 and 7 each in 1 patient and Types 8 and 18 each in 2. Alpha-hemolytic streptococci were the predominant organisms identified in the sputum of 7 of the remaining 9 patients, *H. influenzae* in 1, and *Staph. aureus* in 1. Additional organisms (Table 1) were found in large numbers in the sputum cultures of 10 patients who were considered to have pneumococcal pneumonia. In 2 of the patients with alpha-hemolytic streptococci predominant in the sputum, it was subsequently ascertained that injections of procaine penicillin had been given at home by the physician during the twenty-four hours before admission to the hospital. Clinically and roentgenographically, the pulmonary lesion was considered to be that of lobar pneumonia in 34 cases and bronchopneumonia in 6, of which 4 were classified as pneumococcal pneumonias, and alpha-hemolytic streptococci predominant in the sputum of the other 2.

TABLE 3. *Clinical Effects of Carbomycin Therapy in Patients with Pneumonia.*

CLINICAL EFFECT	NO. OF PATIENTS
Duration of fever (temperature, >99.6°F.)*	
Less than 24 hr.	8
24–48 hr.	13
48–72 hr.	4
4–7 days	9
8 days or longer	4
Duration of acute symptoms*:	
48 hr. or less	7
3–4 days	16
5–7 days	9
8 days or more	6
Effect on white-cell count:	
Below 11,000 after:	
3 days or less	10
4–7 days	10
More than 11,000 after:	
4–7 days	7
8–14 days	7
15 days or more	2
No follow-up counts	4
Persistence of signs in lungs*:	
8–14 days	14 (4)†
15 or more days	4 (3)†
Clearance in 7 days or less	20
Complications:	
Sterile pleural effusion‡	1
Extension to new lobe	2
Atelectasis	4
Meningitis§	2
Duration of hospitalization*:	
7 days or less	5
8–10 days	15
11–14 days	9
15–21 days	4
22 or more days	5
Estimate of benefit from carbomycin:	
Good effect	6
Moderate benefit	15
Indeterminate	8
No benefit	9
Death	2

*Two patients who died both within 24 hours are omitted in these tabulations.

†The numbers in parentheses indicate patients who subsequently received penicillin.

‡First thoracentesis done after penicillin therapy.

§One of these patients also manifested dendritic keratitis.

Dosage

An analysis of the dosage used in all cases is given in Table 2. The antibiotic was given orally in all but 2 patients (including 1 of those considered to be seriously ill), in whom carbomycin treatment was given by the intramuscular route. Oral therapy was initiated with a dose of 500 mg. in each case, and this was usually followed by 2.0 or 3.0 gm. daily given as 250 mg. every three hours or 500 mg. every 4 hours, respectively. In 3 patients in whom the 250-mg. doses appeared inadequate, they were increased to 500 mg. every 3 hours (4.0 gm. daily). The average total oral dose was 14.7 gm. given over a period of 5.7 days; after omission of 10 patients in whom carbomycin was discontinued in favor of penicillin before a therapeutic effect was achieved, this average total dose was 17.0 gm. in 6.5 days.

Clinical Effects

An analysis of the more important effects of carbomycin on the clinical course of the patients with pneumonia is given in Table 3. Defervescence occurred within 48 hours of the first dose in 21 patients, including the 2 who had received procaine penicillin before admission and 1 who was given a large dose of penicillin through a nurse's error after 30 hours on carbomycin therapy when his temperature was rising and he appeared to be getting worse; in 13 patients, however, fever persisted for 4 days or longer. The acute symptoms of pneumonia persisted for 5 days or longer in 15 patients. Pulmonary consolidation or infiltrations cleared, on physical and x-ray examinations, within a week of the beginning of carbomycin therapy in 15 patients, but they were still present during the second week in 18 and after the third week in 4. White-cell counts returned to normal levels within a week after carbomycin was started in 20 patients, but they were last found to be elevated after 4 or more days of therapy in 20 patients and for 8 days or longer in 15. Nine patients required more than 2 full weeks of hospitalization for the pneumonia or its complications.

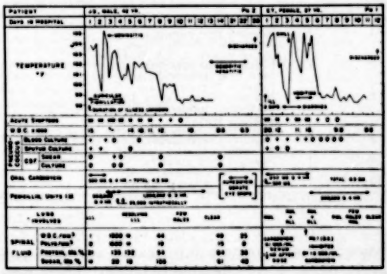

FIGURE 2. *Results of Oral Carbomycin Therapy in Patients J. D. and E. T.*

Complications

One patient had signs of empyema during carbomycin therapy; the first thoracentesis, which was done 3 days after the treatment was changed to penicillin, yielded purulent fluid, which, however, showed no growth on culture. Extension of the pneumonia to adjacent and previously uninvolved lobes was noted during carbomycin treatment in 2 patients, and atelectasis involving the affected lobes in 4.

A diagnosis of meningitis was first established after carbomycin had been started in 2 patients. One of them (Case 18) was seriously ill on admission; he was acutely intoxicated and had previously received considerable sedation. There were no signs of meningeal irritation at the time, but 8 hours later, after he had received 1.5 gm. of carbomycin orally, meningitis was suspected and promptly confirmed by the finding of purulent spinal fluid containing Type 8 pneumococci in abundance. The same organism was cultured from blood obtained at the same time, just before the institution of massive therapy with penicillin. In the second patient (J. D., Figure 2), also an alcoholic who had previously been heavily sedated with paraldehyde, a diagnostic lumbar puncture was done before carbomycin was started, but this yielded normal spinal fluid, which was sterile. Signs of meningitis were first discerned on the third day, 24 hours after carbomycin by mouth had been stopped and intramuscular injection of penicillin substituted. A lumbar puncture done at this time yielded purulent fluid, which showed organisms morphologically resembling pneumococci in smears, but a culture of this fluid yielded no growth.

TABLE 4. *Effect of Carbomycin Therapy on Sputum Cultures.*

Duration of Therapy before Last Positive Culture	No. of Patients	Results of Subsequent Cultures
1	7	Negative after penicillin, 1 case No further cultures, 2 cases Negative (days 2, 3, 4, 7), 4 cases
2	4	Negative after penicillin, 1 case No further cultures, 2 cases Negative (5 days), 1 case
3	6	Negative after penicillin, 1 case No further cultures, 2 cases Negative (days 5, 5, 7), 3 cases
4	1	Negative after penicillin, 1 case
5	2	Negative after penicillin, 1 case (W. L., Fig. 3) No further cultures, 1 case (J. Mc. N., Fig. 3)
6	1	Negative after penicillin
9	1	No further cultures (Fig. 4)
10	1	No further cultures (Fig. 4)

Bacteriologic Effects

In only 3 of the 31 patients whose pretreatment sputum contained pneumococci did the first specimen obtained after carbomycin was started fail to show the same type of pneumococcus. These sputums were obtained 1, 5 and 10 days, respectively, after the first dose, but in the first of these (E.T., Fig. 2), blood cultures obtained on the same day and on the succeeding 3 days all yielded Type 1 pneumococcus. In 5 other patients, including 2 who died, no further sputum cultures were made. A summary of the results of the bacteriologic examinations of sputum for pneumococci in the remaining 23 patients is given in Table 4. Pneumococci were grown from the sputum after 3 or more days of carbomycin therapy in 12 of these patients and after 5 days or longer in 5.

TABLE 5. *Effect of Carbomycin*Therapy on Blood Cultures.**

Case No.	Pneumococcus Type	Duration of Therapy before Last Positive Culture	Results of Subsequent Cultures
		days	
11†	2	2	Negative after penicillin (J. D., Fig. 2)
18	8	½‡	Negative 3 hr. after 1st dose of penicillin; patient died.
23	18	6	Negative after penicillin (W. L., Fig. 3)
39	8	½‡	Patient died; no later cultures
42	1	4	Negative 12 hr. after 1st dose of penicillin (E. T., Fig. 2)

*In 2 patients with positive cultures before carbomycin was started, the first blood culture taken subsequently was negative; in Case 19 (Type 7 pneumococcus) this was done on the 4th day, 12 hours after penicillin was given, and in Case 29 (Type 18) it was done after 2 days (J. McN., Fig. 3).

†Culture of spinal fluid obtained at this time also yielded Type 8 pneumococci.

‡After 600 mg. intramuscularly.

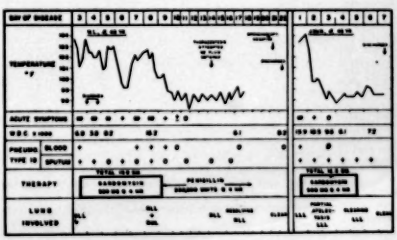

FIGURE 3. *Results of Oral Carbomycin Therapy in Patients W. L. and J. McN.*

Among the 7 patients whose blood cultures were positive for pneumococcus before carbomycin therapy, 5 continued to yield positive cultures for periods up to 6 days or until penicillin was substituted (Table 5). In the 2 remaining patients, the first blood culture obtained during carbomycin therapy (after 2 days of treatment in one and after 4 days in the other) was negative, although sputum

cultures still yielded pneumococci at the time in both cases and continued to do so for several days in 1 of them (J. McN., Fig. 3); in the second patient penicillin was given, and the pneumococci could not subsequently be cultured from the sputum.

Among the 9 patients whose pretreatment sputum failed to yield pneumococci, the alpha-hemolytic streptococci and *Staph. aureus* that were predominant in the original cultures persisted as the predominant organisms throughout the carbomycin therapy; in the patient with *H. influenzae* in abundance in the first sputum, these organisms were not found after 2 days and alpha-hemolytic streptococci became predominant in the sputum at that time.

Various organisms not identified in the original sputum cultures subsequently appeared in moderate or large numbers, some of them in mixed cultures, in sputums obtained during and after carbomycin therapy. These included a large variety of coliform organisms in 15 patients, alpha-hemolytic streptococci in 11, *H. influenzae* in 10, enterococci and *Staph. aureus*, each in 3, beta-hemolytic streptococci (not further identified) in 2 and monilia in 1.

Sensitivity Tests and Blood Levels

Tests for sensitivity to carbomycin were done on 20 strains of pneumococci; the minimum inhibiting concentrations ranged from 0.1 to 0.8 microgm. per cubic centimeter. Six strains were inhibited by 0.1, 5 by 0.2, 7 by 0.4 and 2 by 0.8 microgm. per cubic centimeter. In 1 patient a strain of Type 7 pneumococcus isolated after 4 days of treatment required 4 times the concentration of carbomycin that was sufficient to inhibit the pretreatment strain of the same type tested simultaneously. In a second patient, strains of Type 2 pneumococcus obtained before treatment and after 7 days of carbomycin therapy were equally sensitive. Two strains of *H. influenzae* and 2 of *Staph. aureus*, all of them isolated before treatment, were also tested; 1 of the former was inhibited by 0.4, and the other by 12.5 microgm. per cubic centimeter, and the staphylococcal strains were both inhibited in a concentration of 1.6 microgm. of carbomycin per cubic centimeter.

Concentrations of carbomycin in the blood were determined in several patients; the specimens were obtained at various intervals after therapy was started and at different times after oral doses of the antibiotic. The highest concentration found (by a two-fold broth-dilution method) was 0.5 microgm. per cubic centimeter of serum or of citrated plasma; this concentration was found in a third of the specimens tested. Levels of 0.25 or 0.12 microgm. per cubic centimeter were found in 22 per cent and no carbomycin (less than 0.12 microgm., which was the lowest concentration detectable) could be demonstrated in 44 per cent of the specimens assayed.

Table 6. *Indications for Penicillin in Patients with Pneumonia after Treatment with Carbomycin.*

Case No.	Carbomycin Therapy before First Dose of Penicillin*		Indication for Penicillin
	gm.	days	
1	7.0	2½	Clinical failure; drug toxicity (diarrhea); persistence of pneumococci in sputum.
11†	4.5	1½	Clinical failure; pneumococci persisted in blood and sputum; meningitis developed.
13	14.0	5	Drug toxicity (nausea, vomiting and diarrhea); pneumonia improved.
18	1.5	½	Toxemia increased; meningitis discovered (blood and spinal-fluid cultures positive before first dose of penicillin; patient died 6 hours later).
19	11.0	3½	Poor clinical response; pneumococci persisted in rusty sputum.
22	6.0	3	Drug toxicity (nausea, vomiting and diarrhea); recurrence of fever; persistence of pneumococci in sputum.
23†	19.0	6	Clinical failure; persistence of pneumococci in blood and sputum.
24	0.4 (i. m.)	— (1 dose)	Severe chill ½ hr. after dose; patient's condition appeared to be deteriorating after the chill.
39	1.4 (i. m.)	½	Patient's condition deteriorated progressively; convulsion after last dose (death 8 hours after first dose of penicillin).
41	4.0	1½	Nurse's error (?), but patient's fever was increasing (temperature, 105°F.), and condition was getting worse; pneumococci still present in sputum.
42†	6.5	4	Clinical failure; bacteremia persisted.
43	17.0	6	Slow clinical response; pneumococci persisted in sputum.

*Oral unless otherwise noted.
†Case 11 (J.D.) and Case 42 (E.T.) are depicted in Figure 2, and Case 23 (W.L.) in Figure 3.

Indications for Substitution of Penicillin

There were 12 patients in whom it was believed that continuance of carbomycin therapy was not justified. Penicillin was given to each of these patients in the hope of terminating the infection. The specific reasons for this decision in each case are listed in Table 6.

Estimate of Benefit from Carbomycin

An over-all estimate of the benefit derived from carbomycin was made in each case on the basis of all clinical and laboratory findings (Table 3). About half the patients were considered to have shown

a favorable response to therapy with this antibiotic. Dramatic clinical and bacteriologic effects comparable with those observed quite regularly in similar patients with pneumococcal pneumonia treated with penicillin, aureomycin or terramycin and, in our limited experience, also more or less regularly with adequate doses of erythromycin (3.0 gm. daily by mouth) were infrequently observed; such a response, ascribable to carbomycin, occurred in only 6 patients.

Results in Miscellaneous Cases

The relevant findings in 5 patients who were treated with carbomycin for infections other than pneumonia may be summarized briefly. Two patients were treated for staphylococcal infections,

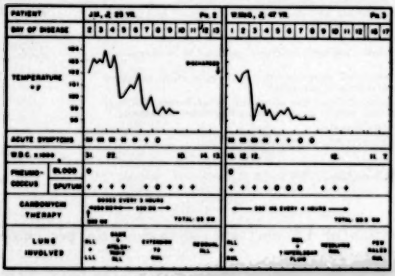

Figure 4. *Results of Oral Carbomycin Therapy in Patients J. M. and W. McQ.*

2 for streptococcal infections and 1 for *Escherichia coli* septicemia and pyelonephritis. Only 1, a patient with acute tonsillitis, possibly benefited from the carbomycin therapy.

Case 8. Carbomycin was given, in doses of 500 mg. orally every 3 hours for 8 days and 100 mg. intrapleurally on each of 4 successive days, to a 53-year-old woman with a staphylococcal empyema complicating an old thoracoplasty. The patient had previously received various antibiotics (other than carbomycin or erythromycin). The strain of *Staph. aureus* obtained in pure culture from the pleural fluid before carbomycin was started was sensitive to 1.6 microgm. per cubic centimeter and one obtained 3 days later was inhibited by 3.1 microgm. There was no significant effect on the clinical or bacteriologic findings, and improvement followed surgical drainage.

Case 16. A 66-year-old woman with *Staph. aureus* bacteremia and pyelonephritis was given 500 mg. of carbomycin orally followed by 250 mg. every 3 hours for a total of 7 gm. in 3 days. Cultures of blood and urine remained positive at the end of this treatment. The patient was then treated with other antibiotics, with some temporary improvement, but she died 2 weeks later. The strains of staphylococci obtained from blood and urine were all inhibited by 1.6 microgm. of carbomycin per cubic centimeter, but assays of random samples of urine obtained during therapy yielded concentrations of only 0.5 to 1.0 microgm. per cubic centimeter and only 0.12 microgm. per cubic centimeter was found in the plasma.

Case 17. A 61-year-old woman with facial erysipelas was treated with 500 mg. of carbomycin orally every 3 hours. The lesion extended slightly during the 1st day, but the patient remained afebrile throughout and the lesion was markedly improved on the 3d day. Preliminary cultures of the nose, throat and cutaneous lesion failed to yield hemolytic streptococci or other pathogens.

Case 34. A patient with acute tonsillitis was given 500 mg. of carbomycin orally every 4 hours for a total of 9 gm. Fever subsided in 36 hours, and symptoms improved in 3 days. Hemolytic streptococci were obtained from pharyngeal cultures before and 24 hours after therapy was started; these were inhibited by 0.4 microgm. of carbomycin per cubic centimeter. The patient left the hospital on the 4th day, and no further cultures were made.

Case 45. A 65-year-old man was started on carbomycin therapy in doses of 500 mg. every 4 hours because of a history of chills and fever and the finding of scattered rales in the lungs. The patient had chronic bronchitis with a mixed flora, but no pathogens in the sputum. He proved to have pyelonephritis and bacteremia; cultures of urine and blood before, during and after therapy with a total of 10.5 gm. of carbomycin were all positive for *Esch. coli*, which were resistant to more than 100 microgm. of carbomycin. Improvement followed treatment with aureomycin and streptomycin, to which the organism was sensitive.

Untoward Effects

The only untoward effects attributable to carbomycin given by mouth were gastrointestinal symptoms; these were noted in 11 of the 43 patients who received the antibiotic by mouth. Nausea and vomiting occurred in 5, diarrhea without vomiting in 4, and nausea, vomiting and diarrhea with abdominal cramps in 2 patients. In 8 patients these manifestations began during therapy with doses of 500 mg. every 4 hours, in 2 others on doses of 500 mg. every 3 hours and in 1 during treatment with 250 mg. every 4 hours. In 4 patients these symptoms, coupled with inadequate response of the infection, were considered sufficient to warrant discontinuance of carbomycin and substitution of another antibiotic. One of the 2 patients who received carbomycin intramuscularly had a chill after an initial dose of 400 mg., the temperature rising to 106°F; the second patient had a convulsion after a 200-mg. dose, the last of 6 intramuscular doses. These reactions may have resulted from inadvertent intravenous injections in spite of the usual precautions to avoid them. No further carbomycin was given these patients.

Discussion

The clinical and bacteriologic results of carbomycin therapy in the patients with pneumonia referred to above indicate that this antibiotic is not highly effective in the treatment of such cases even when used in doses that approach the maximum that is tolerated by most patients. These results are distinctly inferior to those reported in similar cases by many observers with any of the effective antimicrobial agents now in use — namely, sulfadiazine (or related sulfonamides), penicillin, aureomycin, terramycin, chloramphenicol and erythromycin. Persistence of pneumococcal bacteremia in uncomplicated cases of pneumococcal pneumonia

has not been noted during treatment with any of these other agents, but it has now been observed in several such patients while they were receiving carbomycin. In addition, pneumococci persisted longer in carbomycin-treated pneumonias than in those treated with any of the other effective agents mentioned.

Since all the common bacterial pathogens that may cause acute pneumonia, with the possible exception of some resistant staphylococci, are more or less uniformly sensitive to all or most of these agents, and since particularly favorable clinical or bacteriologic results have not been reported with carbomycin in the treatment of various staphylococcal infections, including the 2 cases without pneumonia in the present study, there seems little reason to resort to carbomycin for the treatment of any pulmonary infections. Indeed, in view of the poor results obtained in several of the patients with pneumococcal pneumonia included in the present report and in the one from Syracuse,[17] it must be concluded that carbomycin is definitely contraindicated as the initial or only antimicrobial therapy in pneumococcal infections.

Because the activity of carbomycin against most strains or species of bacteria in vitro is independent of their sensitivity or resistance to the other antibiotics that are in common use, with the exception of erythromycin, carbomycin might be reserved for the treatment of infections with carbomycin-sensitive organisms that are resistant to other antimicrobial agents or for patients known to be hypersensitive to those agents. This offers little scope, since resistance to all the other effective antibiotics in organisms that fall within the bacterial spectrum of activity of carbomycin have been uncommon, except for staphylococci and certain streptococci, and the effectiveness of carbomycin in infections with those organisms has yet to be demonstrated. Moreover, erythromycin, which has an almost identical antibacterial spectrum as carbomycin, has been shown to be appreciably more active in vitro against the great majority of strains[12, 13] and also yields considerably higher concentrations in blood, urine and body fluids.[3, 5, 18-20] Erythromycin therefore appears to be preferable under such circumstances. Furthermore, resistance to carbomycin or erythromycin may readily develop during exposure of many organisms, particularly staphylococci, to either of these antibiotics, and cross resistance between the antibiotics is virtually complete.[12, 14] Nowever, even erythromycin may not give fully satisfactory results in pneumococcal pneumonia under certain conditions.[17]

The failure to demonstrate significant concentrations with any regularity in the blood or urine of patients under therapy and the fact that favorable results appear to be less frequent with this antibiotic than in comparable cases with other effective agents leave little in the way of bacterial infections for which carbomycin can be recommended. The favorable results reported in some cases of urinary-tract infections[15] are inconsistent with the low and inconstant levels of carbomycin found in the urine of those patients or with the results obtained by others.[16] Moreover, since strains of pneumococci are among the most susceptible of bacteria to carbomycin, and since all other antimicrobial agents that are effective against gram-positive coccal infections have produced far superior clinical and bacteriologic effects in patients with pneumococcal pneumonia, it seems unlikely that carbomycin will prove to be very useful for the treatment of any bacterial infections. However, the inhibitory effect of carbomycin in vitro on certain protozoa, including *E. histolytica*,[9] and the favorable clinical effects reported in 5 cases of amebiasis[16] suggest that the potentialities of carbomycin in this and related conditions warrant further exploration.

Summary and Conclusions

The clinical and bacteriologic effects of carbomycin in the treatment of 45 patients are reported. The results in 31 patients with pneumococcal pneumonia appeared to be distinctly inferior to those observed with any of the antimicrobial agents currently recommended for use in these infections. In several of these patients pneumococci persisted in the blood and sputum, and in 2 of them suppurative complications developed during treatment with this drug. There were no favorable clinical or bacteriologic effects in 2 patients with staphylococcal infections.

Concentrations of carbomycin in blood and urine during oral treatment, even with maximum tolerated doses, appear to be irregular and generally lower than those required to inhibit most of the common pathogenic bacteria that can be considered to be sensitive to this antibiotic.

On the basis of the results in these cases and in those thus far reported by others carbomycin cannot be recommended as a useful antibiotic in bacterial infections and is considered to be specifically contraindicated in the treatment of pneumococcal infections.

Untoward effects were limited to the gastrointestinal tract; diarrhea or vomiting, or both, occurred in a fourth of the patients during oral therapy.

We are indebted to Clare Wilcox and Marilyn K. Broderick for technical assistance.

References

1. McGuire, J. M., et al. "Ilotycin": new antibiotic. *Antibiotics & Chemother.* 2:281-283, 1952.
2. Finland, M., and Haight, T. H. Antibiotic resistance of pathogenic staphylococci: study of five hundred strains isolated at Boston City Hospital from October, 1951 to February, 1952. *Arch. Int. Med.* 91:143-158, 1953.
3. Heilman, F. R., Herrell, W. E., Wellman, W. E., and Geraci, J. E. Some laboratory and clinical observations on new antibiotic erythromycin (Ilotycin). *Proc. Staff. Mert., Mayo Clin.* 27:285-304, 1952.
4. Haight, T. H., and Finland, M. Laboratory and clinical studies on erythromycin. *New Eng. J. Med.* 247:227-232, 1952.

5. Smith, J. W., Dyke, R. W., and Griffith, R. S. Absorption following oral administration of erythromycin. *J. A. M. A.* **151**:805-810, 1953.

6. Tanner, F. W., Jr., English, A. T., Lees, T. M., and Routien, J. B. Some properties of Magnamycin: new antibiotic. *Antibiotics & Chemother.* **2**:441-443, 1952.

7. English, A. R., Field, M. F., Szendy, S. R., Tagliani, N. J., and Fitts, R. A. Magnamycin. I. *In vitro* studies. *Antibiotics & Chemother.* **2**: 678-688, 1952.

8. Seneca, H., and Idea, D. Effect of Magnamycin on protozoa and spermatozoa. *Antibiotics & Chemother.* **3**:117-121, 1953.

9. English, A. R., Mullady, H. E., and Fitts, R. A. Magnamycin. II *In vitro* studies. *Antibiotics & Chemother.* **3**:94-98, 1953.

10. English, A. R., Field, M. F., Reilly, J., McNierney, J., and P'An, S. Y. Magnamycin. III. Preliminary studies on absorption and excretion after single dosage. *Antibiotics & Chemother.* **3**:307-313, 1953.

11. Gardocki, J. R., P'An, S. Y., Rapuzzi, A. L., Fanelli, G. M., and Timmens, E. K. Magnamycin: toxicity in experimental animals. *Antibiotics & Chemother.* **3**:55-62, 1953.

12. Welch, H., Randall, W. A., Reedy, R. J., and Kramer, J. Bacterial spectrum of erythromycin, carbomycin, chloramphenicol, aureomycin and terramycin. *Antibiotics & Chemother.* **2**:693-696, 1952.

13. Finland, M., Wilcox, C., Wright, S. S., and Purcell, E. M. Cross resistance antibiotics: effect of exposures of bacteria to carbomycin and erythromycin *in vitro*. *Proc. Soc. Exper. Biol. & Med.* **81**: 725-729, 1952.

14. Finn, J. J., Jr., and Kane, L. W. Magnamycin, new antibiotic: (preliminary note). *Bull. New Eng. M. Center* **14**:113-116, 1952.

15. Trafton, H. M., Lind, H. E., and Correia-Branco, M. Treatment of urinary-tract infections with new antibiotic — Magnamycin: preliminary report. *New Eng. J. Med.* **248**:379, 1953.

16. Hewitt, W. L., and Wood, J. P., Jr. Laboratory and clinical experience with carbomycin. *New Eng. J. Med.* **249**:261-269, 1953.

17. Bunn, P. A. Use of Magnamycin and erythromycin in treatment of pneumococcal pneumonia. *J. Clin. Investigation* **32**:557, 1953.

18. Haight, T. H., and Finland, M. Antibacterial action of erythromycin. *Proc. Soc. Exper. Biol. & Med.* **81**:175-183, 1952.

19. Josselyn, L. E., and Sylvester, J. C. Absorption of erythromycin. *Antibiotics & Chemother.* **3**:63-66, 1953.

20. Kirby, W. M. M., Maple, F. M., and O'Leary, B. Erythromycin serum concentrations following administration in acid-resistant tablets. *Antibiotics & Chemother.* **3**:473-477, 1953.

SPIDER ANGIOMAS APPEARING DURING TREATMENT WITH TRIHEXYPHENIDYL

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TRIHEXYPHENIDYL ([1-piperidyl]-1-phenyl-1-cyclohexyl-1-propanol hydrochloride)† is a relatively effective compound for treating the tremors and muscle rigidity of Parkinson's disease whether due to previous encephalitis or cerebral arteriosclerosis.[1-4] Untoward reactions include dry mouth, nausea, dizziness, blurring of vision, nervousness, tinnitus, generalized pruritus, vomiting, mental confusion, memory impairment and excitement.[2, 5, 6] Pharmacologic studies on laboratory animals reveal that prolonged administration creates no significant alterations in blood sugar levels, phenolsulfonephthalein excretion tests for kidney function and bromsulfalein tests for liver function.[7] Hepatic and renal disorders are reported as not representing contraindications to the use of the drug.[4] Personal observations of a group of patients treated with the drug for relief of Parkinson's disease due to cerebral arteriosclerosis revealed the development of untoward effects in the form of visual and auditory hallucinations, in a number of cases, and of pulsating spider angiomas in 2 cases, which are briefly described below.

Case Report

Case 1. Mrs. A. S., a 69-year-old woman, was first seen in June, 1950, because of symptoms of progressive heart failure of 3 or 4 years' duration. She had also suffered from severe bronchial asthma and hay fever for 55 to 60 years. Extreme shortness of breath had increased in spite of an observation that each attack of asthma had not been as severe as in former years.

The patient had had the usual childhood illnesses; sensitivity to oaks, many flowers and strawberries had been demonstrated on skin testing. She had had diphtheria as a child, without complications, as well as many severe bronchial colds; purulent sputum had been present for a number of years but not for the past 10 years. A complete hysterectomy and appendectomy had been performed in 1918, and tonsillectomy and adenoidectomy in 1928. She had had 4 pregnancies — 3 were full term, and 1 terminated in a miscarriage. Her mother had had asthma and hay fever, as had a first cousin on the mother's side.

Physical examination showed a woman weighing 187 pounds. There was marked cyanosis of the lips and face and engorgement of the neck veins. Examination of the lungs revealed poor aeration, definite intercostal retraction with respirations and diffuse asthmatic rales throughout. The heart sounds were distant; murmurs could not be heard because of the noisy respirations. Examination of the retinal vessels disclosed multiple arteriosclerotic changes. The liver edge extended 3 fingerbreadths below the right costal margin. Pelvic examination was negative. Rectal examination demonstrated external hemorrhoids. The breasts were normal. No abnormal adenopathy was present.

The temperature was 98°F., and the pulse was 74 and regular. The blood pressure was 200/110.

Examination of the blood showed a hemoglobin of 13.8 gm. per 100 cc. (95.2 per cent), a hematocrit of 55 per cent and a white-cell count of 7600, with 66 per cent neutrophils, 27 per cent lymphocytes, 4.6 per cent monocytes and 2.4 per cent eosinophils. The corrected sedimentation rate (Wintrobe method) was 2 mm. per hour. The urine was clear, yellow and acid, with a specific gravity of 1.015, and contained 75 mg. of albumin but no sugar. The sediment contained numerous hyaline casts and 10 to 15 white cells per high-power field. A stool gave a +++ guaiac reaction. A Papanicolaou smear of the cervix was normal. A complete gastrointestinal work-up, including an upper gastrointestinal series, barium enema and sigmoidoscopic examination, was normal. X-ray study of the heart revealed a 30 per cent increase in the transverse diameter. There was prominence in the region of the pulmonary artery, especially on the left. The lung fields showed a general increase in the hilar markings extending outward to both lung fields.

The patient was digitalized fully with digitoxin; ammonium chloride, 5 gm. per day, was ordered, and a low-sodium diet was recommended. Diuresis was dramatic even without the use of mercurial diuretics. The weight decreased to 130 pounds — a most alarming situation as viewed by the patient and her family. ("Loaded with cancer" was their single consideration as cause of the weight loss, so pleasing to the physician.) As the more dramatic symptoms improved, attention was called to a rhythmic tremor of both hands, but more marked on the left, with a suggestive tremor of the head. The patient was started on trihexyphenidyl, beginning with a dosage of 2 mg. a day, with a gradual increase to a maximum of 12 mg. a day. At the end of 10 weeks, she called by telephone to report the onset of an extensive rash. Examination revealed multiple, typically pulsating spider angiomas over the whole face, neck, shoulders and upper part of the chest. There were literally hundreds of such angiomas on the face alone. Since digitoxin‡ and ammonium chloride were thought to be unlikely causes of such a constitutional upset, trihexyphenidyl

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†Artane, available from Lederle Laboratories Division, American Cyanamid Company, New York City.

‡Since the preparation of this paper, LeWinn[8] has described gynecomastia in patients receiving digitoxin.

dyl was presumptively incriminated as the causative agent. The drug was accordingly stopped, and within 3 weeks all traces of the angiomas had disappeared. The patient has been under periodic observation since the appearance of the angiomas in March, 1951. At no time has there been the slightest suggestion of reappearance of this type of skin lesion.

Case 2. W. L. M., a 71-year-old man, was first seen in August, 1951, with the chief complaint of rheumatic symptoms beginning approximately 1 year previously and characterized by painful swelling and stiffness of most of the muscles and joints of the body, particularly those of the fingers, hands, wrists and shoulders. He had also observed an unsteadiness of his gait and of his hands, with an associated tremor dating back approximately 3 or 4 years.

The patient had had the usual childhood illnesses. There had been no serious diseases of any type; a mild attack of influenza had occurred 1 year previously. There was no history of any high fever accompanied by headache or delirium. His father had died at the age of 76 of some prostatic condition; his mother had died at the age of 72 of chronic heart failure; a brother and a sister were living and well. The patient had done carpentry for over 50 years.

Physical examination showed a man weighing 150 pounds, with a rhythmical tremor of the head and neck and of both hands. The fixed, expressionless facies characteristic of Parkinson's disease was present. The pupils were equal and reacted to light. The retinal vessels revealed moderate arteriosclerotic changes, with increased tortuosity, arteriovenous nicking and decrease in the caliber of the arteries. A flexion deformity of the neck was present, accompanying a stooped posture, mostly on the basis of a thoracic kyphosis. Muscle atrophy without fibrillation was observed in the upper arms, shoulders and neck. There was swelling of the fingers, particularly in the region of the interphalangeal and metacarpophalangeal joints. The teeth were carious and fractured. The tongue was coated and the pharynx diffusely reddened. No abnormal adenopathy was seen. The lungs were clear and resonant. The heart sounds were of fair quality and no organic murmurs present. Examination of the abdomen disclosed no masses. The genitalia were normal. Rectal examination demonstrated a smooth, firm, but not hard, slightly enlarged prostate. No masses were felt in the rectum.

The temperature was 98.2°F., and the pulse was 80 and regular. The blood pressure was 190/110.

Examination of the blood showed a hemoglobin of 15.1 gm. per 100 cc. (104 per cent), and a white-cell count of 7600, with 73 per cent neutrophils, 25 per cent lymphocytes, and 2 per cent monocytes. The urine had a specific gravity of 1.012, with a slight trace of albumin but no sugar. The sediment contained no cells.

On August 14 trihexyphenidyl, beginning with a dose of 2 mg. a day, was started. This was increased over a week's time to 2 mg., four times a day for a total of 8 mg. a day. On September 4 the dosage was increased to 5 mg., twice a day. Within 1 week the patient reported "dazzled" vision, inability to focus his eyes and a rough, dry, sore throat. His face was flushed, and the pupils were wide. The tremor seemed less pronounced, except under excitement. The dosage was diminished to 7.5 mg. a day and, because of the dry, irritated throat, was further decreased to 6 mg. a day on November 28. When the patient was seen on May 26, 1952, he had multiple pulsating spider angiomas over the whole face, particularly on the forehead and upper third. The angiomas spread down over the neck and shoulders and the upper anterior portion of the chest. Because of this and the persistence of a dry, raw throat and mouth, medication was changed to caramiphen hydrochloride, with some improvement in the dryness and rawness of the mouth but an apparent increase in tremor and unsteadiness. Within 2 weeks, the spider angiomas had decreased in size and color, and at the end of 1 month they had practically disappeared.

Discussion

The appearance of pulsating spider angiomas in 2 patients taking trihexyphenidyl medication suggested that the drug was the causative agent since a disappearance of the skin lesion followed cessation of this medication. Although liver-function studies were not done, the familiar relation between appearance of angiomas and a state of hepatic insufficiency suggests that liver function was at least temporarily deranged.[9] One suspects that the estrogen level in the circulating blood stream of these patients was elevated. This appears to be one of the currently accepted reasons for the appearance of spiders in pregnancy, chronic hepatic insufficiency, acne vulgaris and anovulatory amenorrhea, and during the adolescent period of both sexes.

Summary

Two cases of pulsating spider angiomas during trihexyphenidyl medication for Parkinson's disease due to arteriosclerosis are presented. The possible connection with temporary liver derangement is briefly discussed.

References

1. Corbin, K. B. Treatment of parkinsonism and related disorders in general practice. *M. Clin. North America* **33**:1131-1139, 1949.
2. *Idem.* Trihexyphenidyl: evaluation of new agent in treatment of parkinsonism. *Collect. Papers Mayo Clin.* **41**:545-547, 1949.
3. *Idem.* Trihexyphenidyl: evaluation of new agent in treatment of parkinsonism. *J. A. M. A.* **141**:377-382, 1949.
4. Doshay, L. J., and Constable, K. Artane therapy for parkinsonism: preliminary study of results in one hundred and seventeen cases. *J. A. M. A.* **140**:1317-1322, 1949.
5. Efron, A. S., and Denker, P. G. Clinical evaluation of certain antihistaminic and antispasmodic drugs in Parkinson's disease. *J. A. M. A.* **144**:5-8, 1950.
6. Phillips, J., Montuschi, E., and Sharkey, J. Artane in treatment of parkinsonism. *Lancet* **1**:1131, 1950.
7. Cunningham, R. W., et al. Pharmacology of 3-(N-piperidyl)-1-cyclohexyl-1-propanol Hcl (artane) and related compounds: new antispasmodic agents. *J. Pharmacol. & Exper. Therap.* **98**:151-165, 1949.
8. Le Winn, E. B. Gynecomastia during digitalis therapy: report of eight additional cases with liver-function studies. *New Eng. J. Med.* **248**:316-320, 1953.
9. Ingelfinger, F. J. Liver. In *Pathologic Physiology: Mechanisms and disease.* Edited by W. A. Sodeman. First edition. 808 pp. Philadelphia: Saunders, 1950.

"THE DOCTOR AND HIS BOOKS"*

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BOSTON

THIS title was used by Harvey Cushing in his address at the opening of the Allen Memorial Building of the Cleveland Medical Library Association on November 13, 1926. That I should quote this great scholar, teacher and bibliophile seems appropriate, particularly since Cushing was greatly interested throughout his lifetime in the Boston Medical Library. He recognized the significance of such an institution in any teaching community, and was himself a great collector of medical literature. Associated as he was, in his formative years, with Osler, Welch, Halsted and Kelly, it is easy to speculate on the influence of these older great physicians in sparking the tinder in Cushing's imaginative and fertile mind. Natural ability, the urge to learn and teach, hard work and constant application eventually elevated him to the enviable position of "the greatest living man in medicine." Although his scientific contributions were original, basic and of lasting importance, his biographic and historical writings are magnificent. The ease with which Cushing's works can be read and enjoyed is a result of the enormous and painstaking effort that he put into them.

It is not my intention particularly to eulogize Cushing but to emphasize the part of a great medical library in the development of men and in the progress of medicine in the community. Every medical student should be looked upon as a potential source for the advancement of knowledge in the prevention and cure of the diseases to which mankind is heir. Teaching institutions, hospitals and research workers are all dependent on an adequate and available supply of reference books and journals. Without these, new and important contributions would be delayed, and recorded data of significance would be overlooked.

It was natural that physicians early in the history of Massachusetts should bring together their own few books on medical subjects and join forces in reading them. They gathered first at each others' homes and furthered their knowledge, scant though it seems today, by discussion and interchange of what they had learned from books and from the behavior of their patients. The first recorded data concerning the early history of the Boston Medical Library refer to 1805, when a formal private medical library was organized. After twenty-one years, normal growth made it necessary to find a fixed depository for increasing material. The Boston Athenaeum took this collection and cared for it until it was transferred to the present Boston Medical Library in 1928.

The first home, being two rooms at 5 Hamilton Place, was outgrown in a period of three years. In 1878 the former residence of Dr. Samuel Gridley Howe, at 19 Boylston Place, was acquired and housed the Library until 1901, when the building now in use at 8 Fenway was constructed and made ready for occupancy. Dr. Howe's interest in afflicted children — the blind, the deaf and the mute should be familiar to many. It was his early efforts to salvage these unfortunate members of society that finally resulted in the great Perkins Institute for the Blind. His wife was Julia Ward Howe, whose fame in the "Battle Hymn of the Republic" days somewhat eclipsed that of her distinguished husband.

In Farlow's *History of the Boston Medical Library*, privately printed by the Plimpton Press in 1918, are to be found many interesting and authentic details about the beginning and development of this institution. Descendants of the original founders are to the present day active in a continuing interest and devotion to this important collection of medical books and papers. It has been said that "books breed books," and so it seems. The growth has been phenomenal. In 1877 the Library was incorporated, and shortly thereafter an inventory revealed 8000 volumes and 5000 pamphlets. Now it has 218,634 volumes and 155,642 pamphlets catalogued, and an estimated 100,000 additional items yet to be filed, so that the Library stands third in size among the medical libraries of the United States, surpassed only by the Armed Forces Library in Washington and the library of the New York Academy of Medicine. Size, however, is of relative importance only, compared to the numerous collections and volumes not to be found elsewhere.

One may question the need of so many books. Are there many duplicates? Are they all still useful? What of their relative importance? These questions cannot be answered accurately. Some duplications are necessary, and some are constantly being weeded out and sold. From thousands of old and useless duplicate journals, pamphlets and some worthless volumes, there is actually a steady small income, since they are sold for old paper.

Shortly after the building at 8 Fenway was occupied, much discussion arose regarding the name. Some of the fellows, preferred then, as some do now, the title of "Academy of Medicine." It is obvious that the Library has in the past fulfilled, and does so now, all the activities of other medical

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academies. From this source all the New England states are served almost exclusively, with the exception of Connecticut, where proximity to New York makes a turning in that direction more feasible. From the beginning, throughout the years and now, this library has been the center of medical progress and graduate education. Since a change of name would have entailed considerable legal difficulties, it did not appear reasonable in the early years of the century to carry this out. It still does not seem important, since the name itself matters little. Actual service to the public and the profession of medicine would probably not be increased or broadened by any such change.

There has always been a close relation between the Massachusetts Medical Society and the Library. Early organizational discussions concerning the Library took place in the rooms of the Society. The Society rented space for its headquarters from the Library for many years, and still holds its larger meetings in the Library's auditorium. It was not, however, until 1947 that the Society voted to join forces completely with the Library so that now all fellows of the Society are members of the Library. This has been a boon to both organizations. Although some of the Fellows of the Society may use the Library little, they are supporting a basic requirement of medical progress. The potential of this aid to medical students and young doctors is incalculable. Physicians give much free service that a few consider to be their fair share in the care of the needy. As a matter of fact, practically all give liberally to charity in addition — often in greater proportion than other segments of society. Of this, they are justly proud, and believe that, as physicians, they stand out in any community primarily as good citizens.

For many years the Massachusetts Medical Society had been accumulating a fund to establish a permanent home. After a careful survey of the problem as a whole, by competent experts, it was decided to purchase the building adjoining the Library and to remodel the interior for this purpose. Now, at 22 Fenway, the Society has a spacious, delightful house for its headquarters. This venture has been entirely successful and satisfactory. At last there is adequate space for the increasing work of the Society. Its connecting door to the Library brings these two great organizations permanently together.

Much study was first made to determine the importance of the Library to the community. Facts regarding the soundness of the building itself and its adequacy for the present and future accumulation of books and other important medical items needed to be assembled. Much of this research was done before the Society finally decided to make the adjoining building into its permanent headquarters. It was found that the present Library building was structurally sound; its architects had planned with vision, and well. The Library had been foresighted enough to purchase an additional lot of land on which was constructed, in the late 1920's, a fine stack wing. Although only the main floor and two-and-a-half modern stack levels were completed, there is adequate space for six-and-a-half more stack levels. This space, when properly equipped, will store all present books safely and conveniently, and allow for the normal growth of the Library for another quarter of a century. Although one may conjecture what will happen beyond that time, it is admitted that twenty-five years is the limit to the foreseeable future in such a project.

It was interesting that there has been a 60 per cent increase in use of the Library in the past five years. This has been accomplished without additional staff, making difficult the maintenance of as good service as the Library would like to offer. In the same period comparable medical libraries did not increase in use but struck a plateau or actually suffered a reduction in their demand for service. Naturally, the possibility of a still further increase in the use of the library is a matter of interest. The peak of service needed in the community may have been reached, but it appears that still greater demands must be provided for.

There has been considerable inertia in recent years in keeping the importance and needs of the Library before the public. The other medical charities in the community, as well as nation-wide movements, have occupied interest. Therefore, the Library has failed to receive its fair share of support. This situation came about insidiously, and in such a manner than no one can be blamed. At present, however, the Library is faced with a serious dilemma: it cannot possibly give adequate service to the medical schools, hospitals, physicians, students, research workers and the public without radical changes and adequate financial aid. Much of the small endowment of approximately $300,000 was given for specific purposes, leaving the income for general expenses far too low to increase the staff or to compensate adequately the few devoted workers. The annual budget is barely enough to keep the Library going, and allows for no improvements whatever. This situation must and will be corrected.

Capital, sufficient to complete the stacks and get the books into modern and efficient locations, must be found at once. The periodical room must be finished to conform to the beautiful and spacious Holmes Hall reading room. Concessions are to be made to the building commissioners. These represent the immediate and urgent needs. To follow closely, a long-range program has been developed to ensure further basic improvements in the build-

ing and to increase the endowment so that more staff members can be employed. This will make it possible to keep the Library open all evenings of the week and provide for better service to the increasing number of eager and sincere seekers after knowledge.

A realization of the worth of this institution is now apparent, and a restitution of the pride that the community formerly had in it. This attitude must be maintained in the future. I am certain that the Library's duty is clear, and that co-operation will be universal.

MEDICAL PROGRESS

THE EFFECT OF AGING OF POPULATION ON GENERAL HEALTH PROBLEMS (Concluded)*

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HEART disease occurs in some form and degree in the majority of aging men and women (Table 6). Many of the greatest advances in internal medicine in recent times have been made in this whole area, and though heart disease remains the leading cause of death, enormous improvements have been made in lessened disability and longer life expectancy. Only a few points need to be emphasized here. Most important is the fact that old people with heart disease are not constantly in danger or disabled by it. Heart failure and coronary-artery occlusion are serious; they may be fatal, but if life continues, compensation is regained and a scar settles down. The chronic disease persists, and yet the heart does a more or less satisfactory job for years. There is no way of predicting when, if ever, a second coronary occlusion will come; it is cruel and futile to proscribe all activity of mind and body because there has been one. There is more to a person than his heart disease; in working with him toward the best general health and performance, the physician often finds that the heart also does better. Another point of interest is the fatigue that weighs on patients who have recovered from heart failure or a coronary occlusion without heart failure. It persists for months; it is greatly in excess of effort; it does not seem to be due to malnutrition unless it may be a protein deficiency; and in old people it is peculiarly depressing. Tests of the efficiency of the heart need to be improved. The standards of vital capacity may have to be modified for aging people, or allowance made for awkwardness and physical unfitness, but even as it is now tested, it is a simple and useful guide. Perhaps the ballistocardiograph will do better. In treatment, it is well to remember that it is not wise to apply the therapy of acute cardiac situations to all who have heart disease or for indefinite periods, with the possible exception of digitalis. The low-sodium diet, the rice diet and the low-cholesterol diet have their uses, but when they are imposed continuously they can lead to malnutrition. This is especially true of old people, in whom nutritional failure is common and attended by serious mental and physical effects. Is it good to lecture old people, publicly and incessantly, on the need for going slow? Do too many of them go fast? And are timid, dependent, old people what the specialist in geriatrics is striving to produce? The better aim is to help them perform well and confidently.

Chronic peptic ulcer of the stomach or duodenum is one of the friendlier chronic diseases. It does not increase in size or severity, though it remains for the life of the patient. Its spectacular complications, hemorrhage, obstruction and perforation, are not as common in the later as in the middle years. The patients do not have more vascular disease than others of their age. Their life expectancy is not lessened. They have long periods of remission. By the time they reach old age the excitants that cause relapses, such as overwork and worry, have faded, and they find relief in simple rules of health, meals at regular hours, adequate rest and exercise. Prescriptions of diets and antacids need not be complex. Acute blood loss can be managed at home if there is some responsible person in attendance and a hospital not too far away should the situation become worse; indeed, intensive hospital care and sudden restoration of blood and fluids seem to prolong convalescence in some cases.

Gallstones are more common in both men and women in their old age than is usually realized (Table 6). It is hard to believe that any medical management of them is of any value. In the Peter Bent Brigham Hospital series, the hospital mortality of old people with gallstones was 34 per cent, whereas the hospital mortality for all the patients was only 23.6 per cent. There were 455 patients who knew that they had gallstones and were not operated upon; of these, 28 died wholly of causes produced by the stones and 53 others died of other diseases with contributions from the stones. This is a medical mortality rate of 17.8 per cent, which far exceeds what should be expected from surgery. Gallstones

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seem to enhance cardiac manifestations in old patients who have heart disease, such as angina and auricular fibrillation. Gallstones and their management increase nervous indigestion. Cancer of the biliary system is not found without them. For all these reasons it is good practice to insist on cholecystectomy soon after the presence of gallstones has been established, and not to wait for complications.

Chronic nephritis is curiously uncommon in old people. The glomerular type is rare, for the kidney tends to become a tubular organ as age progresses. Most of the cases are of the vascular type and are associated with heart disease. There seems to be less uremia than there used to be, and death in old age from renal failure is unusual. Pyelonephritis is a more troublesome form of kidney disease, almost always with infection of other parts of the genitourinary system and with mechanical faults such as stone, relaxed pelvic floor and hypertrophy of the prostate gland.

Hypertrophy and cancer of the prostate gland are important reasons for the inferior situation of men in the seventh and eighth decades of life so far as health and life are concerned. Hypertrophy is not as common as the inexperienced examining finger reports, but still perhaps a fourth of the men over 61 years of age are affected. How much it disturbs them and how long they should go without surgical removal are matters that are unsettled today; my inclination is to advise surgery earlier and more generally. In the Peter Bent Brigham Hospital medical cases, the hospital mortality in 221 patients operated on was 23.5 per cent, — the same as the general hospital rate, — but of the larger group not operated on, 4 per cent died of prostatic disease, and 27.5 per cent more died in part of prostatic disease. Cancer of the prostate, though often detected after metastases have occurred, has come under a surprising degree of control by the removal of sources of male-sex hormone and the administration of female-sex hormone even when the original focus is allowed to remain.

The Peter Bent Brigham Hospital series may be in error in the incidence of diabetes mellitus in old people. It was found in 6.8 per cent of the men and 13.2 per cent of the women, and probably few cases were missed. But the thirty-year survey, which ended in 1943, had fewer patients who were always treated with insulin than any later group will have; there should be more and more well trained diabetic persons entering old age now, and they may modify the clinical picture somewhat. Nevertheless, diabetes seems to be a mild disease in old people. Acidosis is uncommon, and coma is rare. Arteriosclerotic disease of the brain, heart and legs accompanies diabetes in many cases, with unfortunate results, but the association of the two conditions must not be overemphasized. In my series of cases, 40 per cent of the men and 28 per cent of the women had no clinical arteriosclerosis anywhere. Since the carbohydrate defect is not great and immediate regulation is not urgent, and since large doses of insulin have precipitated occlusions in cerebral and coronary arteries, and have caused abnormal motor and mental reactions, it seems wise to modify diet first and to be guided by urinary output of sugar more than by the level of glucose in the blood. Many obese elderly persons with diabetes need no more treatment than a loss of weight and some exercise and added vitamin B complex. If weight reduction proves difficult, one can be sure that the diabetes is unimportant.

Malnutrition is a commoner and more serious problem in old age. Only 20 per cent of the men and women in my series over the age of 61 were moderately overweight, and only 10 per cent could be called obese, whereas 30 per cent of the men and 20 per cent of the women were definitely under normal weight. Nutrition is easily assailed by many chronic infections and diseases that impose inactivity. The amount of weight lost by an edematous cardiac patient is surprising when compensation is restored. The demineralization of bones in plaster casts and on rest in bed is recognized; osteomalacia and osteoporosis are fairly common. But there are other enemies too, such as the absence of teeth and the presence of diseased or poorly placed teeth. Appetite changes when a job, with its regular hours and discipline, is gone. Sadness makes one person a skeleton and another a glutton. People who enter homes for the aged or public almshouses and eat with others who are like what they will soon become, have little zest in eating; so do those who have to eat alone, at home or in unfriendly restaurants. Alcoholism is resorted to by some aging people as a release from sorrow or loss of job. Food fads and fears find an eager audience in old people. Therefore, the prescription of a normal diet is proper, but it does not go far enough. Vitamin supplements are attractive. The really important therapy of malnutrition is unorthodox. It is independence, exercise, occupation, friends to eat with, a good place to live in and good care of disabilities.

Atrophic arthritis rarely begins in old age. Most of the patients suffer only from the mechanical faults and muscle atrophy that were incurred earlier in life. Mild exacerbations of the disease in the joints may follow infections of the respiratory tract or a state of malnutrition. Cortisone and ACTH should not be employed because in these old people it causes high blood pressure and psychotic states. Hypertrophic arthritis can be found by physical examination or by x-ray study in all old people. It seems to be productive of no real difficulty except in the hip joint (malum coxae senilis). Myalgias are common from many causes — bursitis, fibrositis, sprains, awkward use and physical unfitness.

Cancer was found in 13.9 per cent of the Peter Bent Brigham Hospital series, which disregarded

minor growths on the skin because of lack of data. The peak of incidence of cancer in women is reached before the age of 65; in men it comes at that time owing to the frequency of prostatic growths. I know of no formula that will reveal the presence of cancer better than the constant awareness on the part of the family medical adviser that it may be there and the search for it by frequent, thorough physical examinations. How far the search should go involves the art of medicine as well as the cost. Cytologic studies and x-rays are expensive; they leave some sites of possible cancer unexplored. Education of the public to submit to examinations must be done in a manner that will arouse neither unnecessary fear nor impossible hope. Treatment should be thorough, even daring, for cancer grows slowly in old bodies, and palliative measures can lighten the burden of the months or years that remain.

A more serious handicap in the management of the health problems of aging people than lack of information about their diseases is the lack of facilities for their care. At present when old people are sick they are treated at home, or they must go to a hospital, a nursing or old-age home or other institution. All these have serious objections.

Good general hospitals should be available to old people for surgery and for expensive medical studies. They are, but there are too many old people in them. The Peter Bent Brigham Hospital statistics showed that, in 1913, 6.2 per cent of the medical admissions were patients over 61 years of age. In 1943 this proportion had risen to 20 per cent, and a spot survey last fall showed about 40 per cent. The experience of one hospital is not necessarily that of others, and other factors enter in such as the growing use of Veterans Hospitals by young adults and the control of infectious diseases without resort to hospital care. Nevertheless, it seems clear that old people are found in hospitals far in excess of their proportion in the total population. This constitutes a great strain on the hospitals, for many old people cannot pay their full cost and few hospitals are financially able to absorb the difference. Nor have the professional staffs of the hospitals been eager to study geriatrics intensively. The old people are even more unhappy about it because the cost of two weeks' hospitalization takes a large share of their gross annual retirement income. Many of them cannot afford to keep up payments on Blue Cross and Blue Shield when they are allowed to; the price of new subscriptions at that time of life is several times greater. The processes of study can be exhausting, and to misunderstood people they may be emotionally disturbing. When they are discharged from the hospital, continued care at home is commonly so inadequate as to require nursing help or a stay in a nursing home. Three experiments must be made. One is the creation in cities of simple hospitals with reduced charges that can handle those who have illnesses that do not demand complicated studies and those who need short-term care in convalescence from operations and fractures. Another is to see what is the actual cost of a prepaid medical care insurance program for a large cross section of aging people and what device other than charity may be found to help in payment. The third is the development of geriatric clinics in teaching hospitals as foci of investigation.[16]

The mounting burden on mental hospitals of old people committed to them has been commented upon, and also the probability that the burden would be decreased if it were possible to institute medical and rehabilitation services therein. The average age of the old patients on admission appears to be greater than formerly, implying that these hospitals are being used for what they can do under existing circumstances — namely, furnish custodial care. They are somewhat comparable to the chronic hospitals that are adjuncts to county or state homes or almshouses. Terminal care, letting nature take its course with a minimum of assistance from physicians, nurses, dietitians, occupational and other workers and trustees, is sometimes justifiable; more often it is not, and waiting for the end is a grim job for patients and relatives. There are a few places in this country — notably Pittsburgh and New York City — where chronic hospitals are taking long steps forward. Excellent work in England has been done by Dr. Marjorie Warren and others in improving similar conditions, reducing incontinence and restoring personal hygiene and pride; a recent paper by Nisbet[17] has reviewed it.

Nursing homes have become an established facility for long-term care in many parts of the United States, particularly in New England. In Massachusetts there are over 600 licensed nursing homes, the great majority of whose guests are old, and there are also about 800 boarding homes for old people, licensed in nearly the same manner. A few of them are good, and a few can command $10 a day or more, with nursing services extra. Most of them operate in buildings that were not made for their purposes and not altered sufficiently to be efficient or safe even though they have to meet fire-prevention laws; four have burned elsewhere in the United States in the last two years, with the loss of many lives. Most of them have furniture poorly adapted for use by invalids. Most of them are privately owned and without capital resources. Since most of them care for patients supported by public welfare or private charities on fees that do not meet costs that have risen greatly with inflation, they have had to balance their accounts by crowding patients together. Not more than one home in eight has adequate nursing service; nursing assistants have been scarce since stores and factories lured them away. Food is abundant, but diets are not optimal nor are the meals sociable.

The homes are not visited often enough by physicians. Social-work rehabilitation, recreation and connections with neighborhood living are minimal. Nevertheless, the great majority of them perform acceptably an indispensable task. Patients and relatives choose them eagerly in preference to public institutions. The men and women who run them deserve admiration and support. Suitable construction and equipment, active association with hospitals, and provision for convalescence in all its phases should turn them into attractive and competent medical-care units.

Homes for the aged administered by churches, private and fraternal foundations linger on as examples of what genteel charity used to be. A very few of them, notably those under Jewish leadership in Chicago, Cleveland and New York City, are vigorously aware of values hidden in failing old people. Most of them are so short of funds, so restricted in membership because of sex, religious affiliations, character and freedom from disease and financial means and so oriented toward the simplest custodial-care living that the wonder is that they have any devoted apologists today. Old people do not perform well as human beings when they resign the management of their lives to others and commit themselves to almost exclusive association with people similarly old and defeated. It is unrealistic to hope that old-age homes can be transformed. They will remain useful in a narrowing area, just as public almshouses continue to care for those who cannot or do not wish to qualify for private homes.

The important fact forgotten in discussions of old people is that the great majority of them live out their lives in their own homes. The sum of all the people over 61 years of age in Massachusetts who are confined to public or private old-age homes and nursing homes and mental institutions does not equal 5 per cent of that age group. A survey based on the 1950 census[18] showed that 94 per cent of the aged live in households, three fourths of them in their own establishments and one fourth in the homes of nonrelatives. In England, too, 95 per cent of old people live in private dwellings.[19] These are the people with whom one deals in every-day life and whose health problems in all their aspects should be studied intensively. The institutionalized 5 per cent are to be provided for, but forward-looking preventive medicine will concentrate on the 95 per cent. And, again, the general practitioner comes forward as the main resource for a task whose clientele is so vast and so dispersed. So far as I am aware, home-care medical experiments based on hospitals and public clinics do not deal effectively with homes that are composed of one person, which is often the case of the aged.

The economic situation of the 95 per cent of aging people who live independently has a great deal to do with the manner in which they handle their health problems. A brief summary of the facts as given in a bulletin from the United States Department of Labor[6] shows the condition in 1950. The median income of 4,800,000 families whose head was 65 or older was $1903; this was 57 per cent less than the median income of head of families of all ages and 58 per cent less than that of families whose heads were aged 55 to 64 years. This is a drastic reduction in circumstances from what they had been used to, and doubtless it takes place rather abruptly in early old age. Since head of family implies wife or other dependent, a budget of less than $2000 is marginal for city dwellers.

Stated in a broader way, on the basis of money income regardless of home status, the median income of men 65 years of age or older was $986, which is only 38 per cent of the money income of all men over the age of 14 years. Twenty-five per cent of the men 65 years and older had money incomes of less than $500 a year; 50 per cent of them had less than $1000, 71 per cent less than $2000, and only 2 per cent more than $10,000 a year. Of the women who had money incomes, the median at 65 years and over was $531, or 55 per cent of that of women of all ages; the income was less than $500 for 47 per cent, less than $1000 for 82 per cent and less than $2000 for 93.5 per cent. Only 0.4 per cent of women over 65 had incomes greater than $10,000. Ten per cent of all men, young and old, had no money income, but 45 per cent of women 65 years and more had no money income. That is better than the situation of all women over the age of 14, 57 per cent of whom were without income, which, of course, means that their task of running husbands and children is rewarded in a different way and their improved showing in old age discloses their widows' returns from insurance and estates.

This grim summary looks even worse when the sources of money income are identified. Earnings from employment come to only 40 per cent of the 6,000,000 men 65 years of age and over, and to 21 per cent of the 6,700,000 women (this figure is said to include wives of workers). Outside sources of income came to very few men but to 30 per cent of the women. All the others received incomes to which they had contributed nothing or a moderate amount. Old Age and Survivors Insurance, a contributory benefit, came to 28.3 per cent of the men and 19.4 per cent of the women. Veterans' compensation and other federal retirement programs came to 10 per cent of the men and 9 per cent of the women. Public welfare and Old Age Assistance supported 21.6 per cent of the men and 21 per cent of the women.

The majority of the aging population, therefore, are unemployed and living on what is generally called charity. Charity is considered a good thing, particularly by those who give it; it is often necessary, and physicians have always known the joy and the art of administering it. But it is a serious criticism of the economy as a whole that the last third

of life should regularly require it. I cannot help believing that this general need for charity is responsible for a great deal of poor mental and physical performance in old age.

The acceptance of charity may stop a drive to recover thoroughly from illness. It increases the degree of disability caused by chronic disease. It lessens a man's status in his own eyes — often, too, in the eyes of others. It creates dependency; when that persists, fear of return to independence easily follows. Of course, not all old people hate it; neither do all children or adults. The desire to be supported without effort is an immature longing. But many old people have been taught by life that one does not get something for nothing without cost to someone. In their middle age and their independent old age they are so horrified at the prospect of having to take charity and thereby surrender full control of themselves, that its hazard is before them daily, hindering the handling of their jobs, their budgets, their diseases and their associations with the community. They resent the rising costs of charity to which they must contribute. They dislike the public servants who pander to old people by advocating larger benefits earlier in life regardless of need and the professional well wishers who undertake to manage and direct the old people to whom they deal out money and services.

Poverty without charity purchases independence and moral stature at great cost. Symptoms of disease may be ignored because the expenses of diagnosis and care are too heavy. A good diet may be scamped for other budgetary needs. The old home may be lived in long after the physical and economic means to keep it well are exhausted. Vacations may be abandoned because the customary resorts do not fit present capacity to pay. Calls may be limited to clean-shirt day. A cheap home is accepted with isolation from unpleasant surroundings.

Unemployment among older workers has grown steadily for over half a century.[6,20] It lessened during World War II and Korea, but the popular forces strongly favor it. The argument that won the passage of the Old Age and Survivors Insurance and Old Age Assistance laws was retirement at 65 as a means of displacing the old with the more desired young people. Since then pension schemes of all sorts have multiplied. There is grave doubt whether they are able to furnish sufficient money to keep the retirants without further efforts on their part or supplementation from other sources. For example, the average payment under Old Age and Survivors Insurance is now probably about $45 a month; its cost (1950) was $2,100,000,000; to extend coverage to all and raise the payment to $100 a month would not appeal to those who hope for tax abatement. To have $100 a month for life starting at 65 from one's own savings means capital amounting to $17,000; yet more than half of all families have less than $500 in savings. Some industrial pension plans are considered unsound; others will not apply to many contributors because they demand long years of service or because credits are sacrificed when a job is lost before retirement. Where else is support to come from in retirement? Less and less from other members of the family, because of children's needs, commitments to monthly payments on the essential luxuries, small living quarters and dispersion of married sons and daughters.

Witte[20] says that jobs are not the answer, and most experts agree with him. But they have to be the answer. The alternative of charity, even the co-operative sharing of the welfare state, is unacceptable for reasons given above; equally important, a job means occupation, which is a basic human need at all ages. To live is to function. To function as a human being is to be active in things of value to self and to others. To be less active than the physical state permits is conducive to idleness that magnifies problems of mental and physical health. To seek only pleasure or to hold that the world owes one a life of ease because one has worked hard all his life is soon identified as a bitter delusion. Old people, like other normal people, perform best when much is expected of them. Yet there is no simple solution to the question of how to get jobs for old people.

Hobbies can be absorbing to a few. There are a great variety of them. Mr. Allen Eaton[21] has given an entertaining account of handcrafts that can be used to express one large area of creative drives. Others can be found in adult education centers. Those based on the collecting instinct require an outlay of money more than they bring in, and not many old people can afford them. Commonly, they fail to relate the old person to busy people, and most of them are not sufficiently demanding or worth while.

Volunteer work is available to old people in every community. The geriatric clinic of the Peter Bent Brigham Hospital has found a variety of chores for a few of its clients. The patients who have learned to attend regularly and to take responsibility have definitely improved in vigor and confidence, and a few of them have graduated to paying situations. This device can be used more widely to rehabilitate people who have long been off jobs and regular schedules. Most people supported by charity seem to resent being asked to work for no pay; they really mean that they will not exert themselves unless they can improve their social status by doing so. Hence volunteer work, to be effective, must offer either desirable social outlets or possibilities for employment.

Well-to-do old people need occupation just as much, but are not attracted to uninteresting tasks. What many of them find is not very satisfying. Hall[22] has written about the problems of retired business executives. He reports that only about

10 per cent of them perform services of value to their community comparable to those which they had rendered when they were employed. That is an indictment that hits everyone. There is a great deal of important work that needs to be done but that can offer no money: trusteeships of schools, hospitals, institutions; research for public and private institutions to show what work they are doing, its results and desirable changes; and collection, evaluation and dissemination of information about local, county and state activities. To start such projects in a way that would attract capable men and women in sufficient numbers is difficult because it has been done so little and with scant imagination.

Arguments about the place of the older workers in industry run into a maze of contradictory evidence that is full of misinformation and bias for or against. Burns and Brown have summarized the facts fairly well in a chapter in Cowdry's *Problems of Ageing*.[7] The assets of the older worker such as experience, less absenteeism, less spoilage and fewer accidents, are supposedly offset by slowness and hazards of liability for long-lasting disablement and short contributions to pension schemes; here the tendency is to see only big business and masses of workers, not the greater freedom of little business. The question of retirement at 65 years of age has developed curious facets: the large company, pictured as paternalistically responsible for the welfare of its retired workers until their death; the supposition that physicians are able to identify workers who can continue to work and those who must be retired early; the suggestion that a committee of personnel men and psychologists could do this; the hope that aging workers would happily agree to taking lesser jobs or shorter hours or less pay; and pensions made subject to agreement not to work in that company or any covered employment again, as in Old Age and Survivors Insurance. What right has the Government or any company to forbid or to limit gainful occupation if contributed insurance is due? Compulsory retirement at a stated chronologic age seems to me equitable and valuable for both companies and colleges; it assures the development of successors and desirable changes in administration, and the retirant can look forward to a time when he can be relieved of the mounting burden of committee meetings, public relations and executive tasks that interfere with the work he wants to do. But why discard professors and vice-presidents totally when they become emeriti? My conviction is that the retirement crisis is far more serious and common than people realize. It is not measured only by the few who die or become incapacitated soon after they retire. It colors many of the actions and decisions of important officials for years before, because they see nothing interesting for the rest of life. It begins even at 40 or 45 years of age for those who are rejected for jobs because they are too old. Poor performance at 60 is often due to fatigue and tension, and at 67 there comes a new vigor that finds no outlet.

These questions, involving the independence and mental and physical health of millions, will not be solved easily, but a mechanism is now being fashioned that can help. The Sunset Industries was established this year to provide jobs for people over 60 years of age. Being a nonprofit corporation, it can pay its workers without their sacrificing pensions from Old Age and Survivor's Insurance. It is confident that it can do better than meet the minimum wage requirement; should profits mount up, they will be distributed as fringe benefits. It has obtained subcontract work from a number of companies, and as capital becomes available, small factories will be readied for sewing, wood working and clerical projects. One is now in operation in Haverhill, Massachusetts, employing 14 women ranging from 60 to 73 years of age in the making of blouses and pajamas. By the end of the year it hopes to have 200 old men and women at work in Boston and other cities in New England. Its board of bankers, industrialists, labor-union leaders and public servants is determined to find an answer to the staggering costs and implications of welfare taxes. The members of the board do not know all about old people, but they have a curious eagerness to face difficulties.

However, Sunset Industries cannot for the present employ old people who are untrained or who have physical limitations. Later on, it hopes to experiment in the area of part-time jobs and home-based or sheltered work. But other facilities will be needed to educate and fit old people for full employment of their own choice. Men who cannot re-enter the field of their younger days should be studied for alternative aptitudes and should be taught how to use them. Many women, regardless of early education, have no salable skill except housekeeping when they are widowed; they should find schools where they can learn trades or services more to their taste and capacity. Old people are permitted to enroll in public and private adult education programs, but I do not know of any place where they are well cared for. The fact is that one does not know how to teach old people, what to teach them and how to revivify them. It ought to be possible to do so. Physicians know that they must study all their lives if they are to perform well. Other people are not aware that they must do so too. Quite possibly, it may turn out that the general inferior view of old age is the result not of years or disease but of habits of physical and mental slackness. What would a democracy become that sustained and utilized the drive of all its senior citizens?

Housing is another factor that affects the health of the aging. Many old people own their own homes, and for many of these such a possession not only increases their sense of security but also reduces their need for cash and gives them work and hobbies.

Even badly dilapidated houses are not to be criticized without reflection whether the occupants are better as total persons than the well tended inmates of institutions. But a castle can become a liability when the cost in money and strength to keep it up is too great, or when it has not a freely swinging door to the neighborhood. Tenants of apartments in cities are in trouble financially because rents take more than the formerly accepted ceiling of 25 per cent of income. Good apartments are beyond their means or too large, or too far above ground, or too noisy with children and radios. There is no use in concealing the facts that several generations do not behave amicably under one roof and that communications between tenants are less than those who are old and lonely desire. Occupants of single rooms are still worse off, whether they have to go out to meals or down to a common boarding table. They are concentrated not in slum areas of cities but in the adjacent inferior neighborhoods. Two years ago a superficial survey[23] showed that there were 6000 persons in the South End of Boston over 65 years of age; three fourths of them were single, one fourth were married couples and more than half were on Public Welfare and Old Age Assistance.

How to provide good housing at costs that independent old people can pay is a question that has not found an answer. There is so much talk that lacks knowledge of what old people are and want — proposals for congregate homes in Florida for retired labor-union members, plans for co-operatively owned apartments in the West and so on. Public housing for the aging in Denmark is isolated from other people's homes. In Sweden, three grades of living were provided for old people, — apartments for the well, custodial care for the disabled and a limited service home for the in-betweens, — but it was found that the last was not used, the old people clinging to independence to the last moment. It is hard to protect old people from the emotional officiousness that would put them in homes among the birds and nature when they long for close proximity to the rich life of the city, or would give them ramps for stairs and so increase their difficulty with balance and stiff hips. An interesting experiment was launched recently by the Commonwealth Housing Corporation. It has accepted funds to build an apartment house in Boston consisting of one-room and two-room completely equipped apartments for 400 people over 60 years of age. There will be no bar because of color or race or family status, but those on Old Age Assistance must be limited to not more than one fourth of the total because the estimated rentals will run higher than Old Age Assistance can pay. The building will contain also a cafeteria for tenants and neighbors, a lecture-play room and common rooms; an independent nursing home is planned next to it.

Finally, it needs to be pointed out that normal living in old age requires the other facilities that younger people take for granted. Good nutrition demands not just food that is good for one but people to share it with. Eating alone in a room, in a hotel dining room with only the waiter interested in one or in a noisy cafeteria is not conducive to appetite and digestion. Might there be a revival of the early American boarding house or the later eating clubs? Good housekeeping may demand help; can ways be found to buy it economically for the one hour daily or weekly that may be enough? Boston has a few successful old-age clubs; they need to be expanded in number and range of services to provide independent solitary people with stimulating companionship. The Golden Age Clubs of Cleveland[24] have reached a large membership. Vacations are essential, even in retirement, to restore mental and physical elasticity, but they are within the reach of only a few, and for very short stays.

Summary

An attempt has been made to describe old people and their problems. Clinical studies are needed to find how best to identify and treat their acute diseases as well as their chronic illnesses and their persistent mental and physical disabilities. It is probable that much would be accomplished if ways could be found to keep them active, free from charity and housed independently in full association with the community of their choice. For the majority of old people have the capacities and aspirations of normal human beings.

270 Commonwealth Avenue

References

16. Monroe, R. T. Medical problems of old age. *New Eng. J. Med.* 240: 57-60, 1949.
17. Nisbet, N. H. Some practical considerations in care of old. *Lancet* 1:184-190, 1953.
18. Facts on housing for aging. In *Proceedings of the Fifth Annual Conference on Aging.* Ann Arbor, Michigan: University of Michigan, July, 1952.
19. *Old People. Nuffield Foundation. Survey Committee on the Problems of Aging and the Care of Old People.* 202 pp. London: Oxford University Press, 1947.
20. Witte, E. E. Social provisions for aged. In *The Aged and Society.* Champaign, Illinois: Industrial Relations Research Association, 1950. Pp. 115-136.
21. Eaton, A. H. *Handicrafts of New England.* 374 pp. New York: Harper & Brothers, 1950.
22. Hall, H. R. *Some Observations on Executive Retirement.* 298 pp. Cambridge: Division of Research of the Harvard Graduate School of Business Administration, 1953.
23. Powell, A. Personal communication.
24. Woods, J. H. *Helping Older People Enjoy Life.* 139 pp. New York: Harper & Brothers, 1953.

MEDICAL INTELLIGENCE

INTRATHORACIC HIBERNOMA*

Third Reported Case

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NEW ORLEANS, LOUISIANA

HIBERNOMA is the term applied to a rare tumor composed of multiloculated fat cells morphologically similar to, if not absolutely identical with, the cells of the so-called "hibernating gland"of animals. Although evidence for the existence of a homologous structure in human beings is controversial, in embryos and occasionally in adults a tissue indistinguishable from hibernating-gland fat, even to its brown color, is found. The exact relation between this "brown fat" and adult adipose tissue has never been adequately clarified, some writers adhering to the concept that brown fat represents mere remnants of a phase in the development of yellow adipose tissue,[1-5] and others preferring to regard it as a special tissue that, although arising from embryonic fat, has become clearly differentiated from ordinary fat and may be related to a special organ comparable to the hibernating gland.[6, 7] Whatever its origin, the evolution of characteristic tumors from this structure has become well validated, largely as the result of a superb review of the subject in 1949 by Brines and Johnson,[7] who were able to authenticate only 9 hibernomas from the entire world medical literature. To these they added a case of their own, which together with those subsequently reported,[7, 8, 9-10] brings the total to 18. The case reported below is thought to be the nineteenth reported hibernoma and only the third arising within the chest.

Case Report

H. L. T. (V. A. H. 28962), a 31-year-old Negro hospital attendant, was admitted to the hospital on June 20, 1951, for evaluation of a slowly enlarging radiographic density in the peripheral margin of the left-upper-lung field. He had first been seen 3 weeks previously complaining of pleuritic pain in the precordial area that had spontaneously subsided in the interim. He denied any other symptoms related to the chest. The past history and system review were noncontributory, including a denial of antecedent trauma. He was afebrile, and physical examination was negative in all respects.

Various laboratory examinations were either negative or within normal limits. Tuberculin and histoplasmin skin tests were both strongly positive; a coccidioidin skin test was negative. No abnormalities were noted at bronchoscopy.

A posteroanterior roentgenogram of the chest taken with the patient erect revealed a smooth, round, sharply demarcated

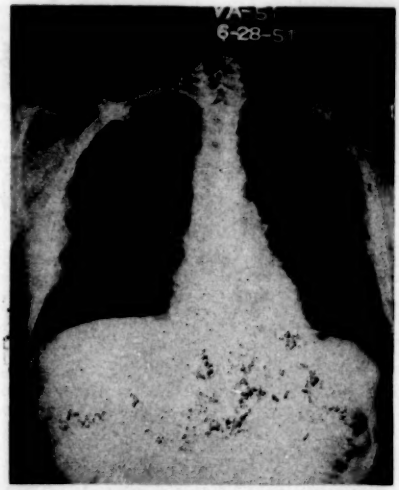

Figure 1. *Posteroanterior Roentgenogram, Showing the Smooth, Rounded Appearance of the Tumor and Its Proximity to the Left Axilla.*

opacity measuring 4 by 3 by 2 cm. located along the lateral margin of the 1st left anterior intercostal space (Fig. 1). It appeared to arise from the pleura and occupied a posterior position on lateral view. The remainder of both lung fields appeared normal. A review of the patient's previous films showed the lesion to be visible in retrospect as far back as 1947, when it had been a third its present size. The initial impression, of both the radiologic and the chest service, was that this probably represented a benign pleural mesothelioma on the basis of its circumscribed character and intimate relation to the pleura. A neurofibroma was considered a 2d possibility.

Although the lesion was unanimously deemed benign, its increasing size prompted an exploratory thoracotomy. On July 16, with the patient in the right lateral recumbent position under cyclopropane-oxygen-ether endotracheal anesthesia, a classic left posterolateral thoracotomy incision was made, and the pleural space entered through the bed of the subperiosteally resected 5th rib. After a Finochietto rib retractor had been inserted, a firm, round tumefaction was noted high within the thorax overlying the 2d rib. By incising the parietal pleura, the margins of the tumor were delineated and the mass was excised by both sharp and blunt dissection. It did not appear to be fixed to the overlying pleura, rib or intercostal muscles. Hemostasis at the tumor site was assured, and a final inspec-

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tion of the lung and pleura revealed no further abnormalities. The chest was then closed in layers without drains, the patient having tolerated the procedure well. The subsequent course was entirely uneventful, and he was discharged on the 10th postoperative day. Over the ensuing 18 months' follow-up period x-ray films have shown no recurrence.

On gross examination the fresh surgical specimen consisted of a section of pleura measuring 3 by 5 cm. with an attached tumor mass measuring 3.5 by 3 by 1.4 cm. The overlying pleura contained a 2-cm. yellowish plaque. The tumor mass had a spongy consistence and appeared finely lobulated. On cut surface it was tawny, brownish-yellow and greasy to the touch. A thin capsule surrounded the entire tumor.

On microscopical examination the tumor was divided into multiple lobules by delicate, moderately vascular, fibrous septums. The lobules comprised 2 distinct types of cells, the predominant but smaller cell (20 to 50 microns) being multilocular with central nuclei, and the less numerous but larger cell (50 to 75 microns) appearing to be ordinary unilocular fat cells with typical signet-ring nuclei. The multilocular cells were polygonal or ovoid in shape and exhibited considerable variation in size. They tended to occur in closely packed masses separated by interspersed adult fat cells. The cell membranes were extremely well defined. The cytoplasm was eosinophilic and gave the impression of granularity owing to the presence of many small vacuoles measuring 2 or 3 microns in diameter (Fig. 2). Less commonly these cells presented a finely fibrillated appearance that suggested a transition between the multilocular and adult adipose cells. The nuclei of these brown-fat cells were round and basophilic and contained one or several nucleoli. Most of the nuclei were central or only slightly eccentric in position. Oil red O stain for fat showed the vacuoles to consist largely of lipoid material. A chemical analysis of the tumor tissue was not done.

The diagnosis was intrathoracic hibernoma.*

*Confirmed by Dr. Osborne A. Brines.

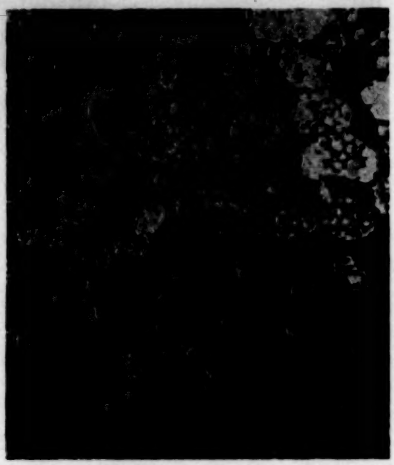

FIGURE 2. *High-Power Photomicrograph of the Hibernoma, Showing Characteristic Granular and Multilocular "Brown-Fat" Cells.*

Fusion of vacuoles within some cells suggests a transition to adult fat cells.

DISCUSSION

A gland-like organ peculiar to many but not all hibernating animals, and a number of nonhibernating animals as well, has long been recognized but remains poorly understood. In gross appearance this so-called hibernating gland is a lobulated, highly vascular mass that is light brown, this color apparently reflecting its high lipochrome content.[7] Microscopically, hibernal tissue is characterized by a unique type of cell, half the size of an ordinary fat cell and containing multiple, small fat droplets rather than the solitary, large fat globule of mature adipose cells, and a round, centrally placed nucleus instead of the usual peripherally situated, signet-ring nucleus. For our knowledge of the anatomic distribution of the animal hibernating gland, we are primarily indebted to Rasmussen[1] (1923), who, by correlating existing information with an intensive study of his own, was able to demonstrate bilateral projections of brown fat from a primary mass in the superior mediastinum into the axillas, neck, back, perirenal and retroperitoneal tissues and even into the inguinal and gluteal regions.

In 1902 Shaw,[11] after a careful study of the fat of the human fetus, demonstrated that the axillary and subpleural adipose tissue originally consisted largely of brown fat, in contrast to the yellow fat of fetal subcutaneous tissue. Hatai[12] simultaneously pointed out the presence of a gland-like mass in the interscapular region of human embryos that appeared identical to the animal hibernating gland. A few years later Bonnot[13] confirmed the existence of such a gland and demonstrated its persistence into adult life. He showed that it was by no means limited to an interscapular position, but could be found in approximately the same localities that its proposed homologue occupied in animals. Whether the presence of such a mass of brown fat can be interpreted as the equivalent of a hibernating gland, or whether it represents merely the remnants of a phase in the development of adult fat is open to question. Brines[14] concludes that there is insufficient evidence to state categorically that such a thing as a hibernating gland or its counterpart does or does not exist in human beings, but he leans toward the view that the hibernoma is a distinct entity and may be related to a special organ, which at least theoretically is the hibernating gland.

If one accepts the evidence for the existence of a human hibernating gland, the foregoing anatomic studies suggest that tumors arising from this organ should be confined to fairly well defined sites. For the most part this has proved true. Thus, the tumor was situated on the posterior aspect of the chest in 4 of the 18 reported cases,[2, 5, 7, 15] in the axilla in 3,[10, 16, 17] within the chest in 2[9, 10] and in the posterior part of the neck,[8] popliteal space[3] and lumbosacral region[4] in 1 each. On one occasion the

location was not defined further than "back,"[18] and in 5 others[19, 20-22] the site was not mentioned. The case reported above, although intrathoracic, was closely juxtaposed to the left axilla. Worth noting is the fact that no mediastinal hibernoma has been reported, for on theoretical grounds this is a likely site.

All recorded cases have involved benign, solitary lesions. In the subcutaneous tumors the clinical diagnosis has almost invariably been a lipoma. In both previously reported intrathoracic hibernomas[9, 10] the preoperative diagnosis was neurofibroma. The intimate relation to the pleura that characterized the case described above prompted a clinical diagnosis of a fibrous pleural mesothelioma, a neurofibroma being considered as a second possibility.

In the treatment of these tumors surgical excision seems advisable on the basis of their clinically indeterminate nature alone. Moreover, the large proportions attained by the intrathoracic hibernoma reported by Kittle, Boley and Schafer[9] is ample testimony of the necessity for resecting those within the chest. Malignant transformation is a hypothetical possibility so far unreported.

Various authors[7, 9] have stressed the importance of distinguishing the hibernomas from atypical lipomas, xantholipomas, myxolipomas, lipoblastomas and granular-cell myoblastomas. In addition, on gross examination several authentic hibernomas have borne a close gross resemblance to cystic lymphangiomas.[7] The brownish color imparted to most hibernomas is a significant feature that should arouse one's suspicion, but it must be noted that this characteristic is by no means constant, as typified by the case reported by Rasor,[18] in which the tumor appeared milky white. Cases such as the one presented above and those of Simon[8] and Rasor,[18] in which all stages of transition between embryonal and adult fat were exemplified, illustrate how easily a hibernoma might pass for a lipoma if the histology were not carefully scrutinized. At the same time, however, such cases suggest a close relation of the hibernoma to ordinary lipomas. Attempts have been made to distinguish hibernomas from lipomas by chemical analysis, but the results have been inconclusive, although a high unsaponifiable fat fraction — considerably higher than that of analyzed lipomas — has been demonstrated in several hibernomas.[7, 10]

The function, if any, of human brown fat is unknown. Despite a considerable amount of investigation the exact role of the animal hibernating gland also remains, in part at least, enigmatical. The idea that it serves during hibernation as a reserve store of food has been disproved,[1] but there is some evidence that it may exert an endocrine control during hibernation by suppressing body metabolism and thus conserving energy.[23] Actually, a relation to the endocrine system has long been suggested, because of its resemblance to the fatty, involuted thymus and the vacuolated cells of the adrenal cortex.[24, 25] As Sutherland et al.[3] have pointed out, there are a number of experimental studies in support of this concept. Thus, the androgen content of hibernating glands from both male and female woodchucks killed during the summer approximates that of the bull testis.[26] Selye and Timiras[27] observed the rapid disappearance of lipid and glycogen granules from the brown fat of rats during the alarm reaction, and they regard this phenomenon as one of the most sensitive indicators of diseases of adaptation in animals. The injection of excessive quantities of cortisone into mice is followed by a decrement in the size of both the hibernating gland and the adrenal glands.[28] Although brown fat is too widespread to permit consistently successful extirpation experiments, Vignes[29] found that complete removal of the gland usually caused the death of the animal. In 2 hibernomas Gross and Wood[10] recently identified a significant quantity of birefringent crystals similar to those previously described in the adrenal glands.[30] Although these experiments fail to fathom the precise function of the hibernating gland, they suggest certain endocrine relations. So far as human hibernomas are concerned, neither their presence nor their removal has yet been accompanied by any abnormality suggesting an endocrine effect.

Summary

An intrathoracic hibernoma is reported, representing, it is thought, the nineteenth proved case of this interesting neoplasm, and only the third arising within the chest.

The literature on hibernomas is briefly reviewed, and the possible relation between these tumors and the so-called hibernating glands of animals is discussed.

We are indebted to Miss Elizabeth Shoughro, medical librarian, for her assistance in reviewing the literature, and to Mr. Frederick W. Busic for preparation of the illustrations.

References

1. Rasmussen, A. T. So-called hibernating gland. *J. Morphol.* **38**: 147-205, 1923.
2. Sieber, W. K., and Heller, E. L. Hibernoma: unusual location in popliteal space. *Am. J. Clin. Path.* **22**:977-980, 1952.
3. Sutherland, J. C., Callahan, W. P., Jr., and Campbell, G. L. Hibernoma: tumor of brown fat. *Cancer* **5**:364-368, 1952.
4. Wegener, F. Braunes Lipom und braunes Fettgewebe des Menschen. *Beitr. z. path. Anat. u. z. allg. Path.* **111**:252-266, 1951.
5. Miller, J. R., and Docherty, M. B. Interscapular hibernoma — report of case with brief review of literature. *California Med.* **77**: 38-40, 1952.
6. Shattock, S. G. On normal tumour-like formations of fat in man and lower animals. *Proc. Roy. Soc. Med.* (Path. Sect. Part 3): 3:207-270, 1909.
7. Briney, O. A., and Johnson, M. H. Hibernoma, special fatty tumor: report of case. *Am. J. Path.* **25**:467-480, 1949.
8. Simon, H. E. Posterior cervical tumor of brown fat in man: its relationship to interscapular gland of hibernating animals. *Am. J. Surg.* **80**:127-130, 1950.
9. Kittle, C. F., Boley, J. O., and Schafer, P. W. Resection of intrathoracic "hibernoma." *J. Thoracic Surg.* **19**:830-836, 1950.
10. Gross, S., and Wood, C. Hibernoma. *Cancer* **6**:159-163, 1953.
11. Shaw, H. B. Contribution to study of morphology of adipose tissue. *J. Anat. & Physiol.* **36**:1-13, 1902.
12. Hatai, S. On presence in human embryos of interscapular gland corresponding to so-called hibernating gland of lower animals: preliminary communication. *Anat. Anz.* **21**:369-373, 1902.
13. Bonnet, E. Interscapular gland. *J. Anat. & Physiol.* **43**:43-58, 1908.

16. Brines, O. A. Personal communication.
15. Inglis, K. So-called interscapular gland and tumors arising therein. *J. Anat.* 61:452-466, 1927.
16. Bonnel, F. Tumeur du creux de l'aisselle. *Bull. et. mém. Soc. anat. de Paris* 89:110-112, 1914.
17. Mosto, D., and Radice, J. C. Hibernoma de Gery. *Rev. med. y cirn. afines, Buenos Aires* 8:61-68, 1942.
18. Rasor, H. Über ein Lipom des Erwachsenen mit Lipoblasten in verschiedenen Stadien. (Inaugural dissertation, Heidelberg University.) Wiesbaden: Bergmann, 1913. Pp. 1-10.
19. Merkel, H. Über ein Pseudolipom der Mamma. (Eigenartiger Fettzellentumor.) *Beitr. z. path. Anat. u. z. allg. Path.* 39:152-157, 1906.
20. Gery, L. Discussion of Bonnel.[16]
21. Annual Meeting Notes. Pathological Museum. *Brit. M. J.* 3:212, 1921.
22. Rochat, R. R. Hibernom. *Acta uberl. Morph.* 3:301, 1939.
23. Hook, W. E. Effect of crude peanut oil extracts of brown fat on metabolism of white rat. *Proc. Soc. Exper. Biol. & Med.* 45: 37-40, 1940.
24. Cramer, W. Glandular adipose tissue; its relation to other endocrine organs and to vitamine problem. *Brit. J. Exper. Path* 1:184-196, 1920.
25. Wells, H. G. Adipose tissue, neglected subject. *J. A. M. A.* 114: 2177-2183 and 2284-2289, 1940.
26. Sweet, J. E., and Hoskins, W. H. Androgen in woodchuck hibernating gland. *Proc. Soc. Exper. Biol. & Med.* 45:60-62, 1940.
27. Selye, H., and Timiras, P. S. Participation of "brown fat" tissue in alarm reaction. *Nature* 164:745, 1949.
28. Antopol, W. Anatomic changes produced in mice treated with excessive doses of cortisone. *Proc. Soc. Exper. Biol. & Med.* 73: 262-265, 1950.
29. Vignes, H. Quoted by Brines and Johnson.[9]
30. Ayres, W. W., Firminger, H. I., and Hamilton, P. K. Birefringent and sudanophilic lipoids in adrenal cortex in disease and sudden death. *Mil. Surgeon* 109:503-517, 1951.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 39341

PRESENTATION OF CASE

A fifteen-year-old girl was admitted to the hospital because of "fainting spells."

The patient had been in good health until she was about five years of age, when a diagnosis of rheumatic fever was made. She was hospitalized for a year and examined annually thereafter, without evidence of recurrence or the development of murmurs. She entered school at the age of seven, and in the next few years cyanosis of the lips and nail beds gradually developed. Although she was moderately active during this time she became short of breath, tired easily and was unable to keep up with the activities of her playmates. Five years before admission she experienced her first syncopal attack, which occurred while she was recuperating from an appendectomy, and was asked by a nurse to sit up. She had suffered similar attacks about every two or three months since then, and these seemed to be related to overexertion and emotional upsets such as arguments with the family. They also came on when she "read too long," and were usually followed by a throbbing headache, chiefly over the vertex, that was relieved by lying down or sleeping. Six months before entry the family moved to another state, and the patient had considerable difficulty adjusting herself to the new surroundings, particularly to her schoolwork. Since that time she had experienced increasing exertional dyspnea accompanied by cyanosis, frequent headaches and weakness in the legs. Fainting spells now occurred about once each day. She became dyspneic on climbing only a few stairs, and fainted when walking up two flights. Three weeks before examination her mother was hospitalized for a major operation, and during this time the patient had only one fainting spell.

There was no history of orthopnea, paroxysmal nocturnal dyspnea or peripheral edema. During the two months before admission she had lost 10 pounds in weight.

Physical examination showed a well developed girl in no distress. There was cyanosis of the face, lips and nail beds, and clubbing of the fingers. The eyes were normal. The lungs were clear. The point of maximum impulse of the heart was felt in the midclavicular line. There were no thrills. The pulmonic second sound was very loud and inconstantly split, and its impulse was easily palpable. There were two heart sounds in systole in the pulmonary area. No murmurs were heard. The rest of the examination was negative.

The temperature was 99°F., the pulse 100, and the respirations 20. The blood pressure was 105 systolic, 80 diastolic, in the right arm, 110 systolic, 75 diastolic, in the left arm and 120 systolic, ? diastolic, in the right leg.

Examination of the blood revealed a hemoglobin of 17.7 gm. per 100 cc. and a white-cell count of 11,900, with a normal differential. The hematocrit was 61.5 per cent. In a roentgenogram of the chest the heart was not enlarged, but the main pulmonary artery appeared prominent (Fig. 1). The right ventricle appeared to be slightly enlarged on a lateral view (Fig. 2). The lungs were normal. An electrocardiogram disclosed a sinus arrhythmia at a rate of 65 per minute and right-axis deviation. The PR interval was 0.14 second, and the QRS interval 0.08 second. The P waves appeared normal. There was a small Q wave with tall R waves and inverted T waves in Lead V_1. The R waves were prominent in Lead V_5. On the fifth hospital day an arm-to-

tongue circulation-time determination was carried out; 1 cc. of Decholin was injected on two occasions, one minute apart. A good end point was achieved each time at seven and eight seconds respectively. About five or ten minutes after the injection the patient became markedly dyspneic and restless, and more cyanotic than usual. A short while later she became unresponsive and had a brief generalized tonic-clonic convulsion, followed by a period of apnea. The pulse was 70 per minute, and the blood

FIGURE 1.

pressure 180 systolic, 120 diastolic. Respirations were restored for a short time after artificial respirations but soon failed, along with the pulse. Intravenous administration of calcium chloride, intravenous and intracardiac administration of epinephrine, cardiac massage and electrocardiac stimulation were to no avail, and the patient was pronounced dead about forty-five minutes after the onset of the acute episode.

DIFFERENTIAL DIAGNOSIS

DR. DAVID LITTMANN*: This girl of fifteen was admitted to the hospital for fainting spells and cyanosis. At the age of five she had had rheumatic fever, which must have been severe because she was kept in the hospital for a year. It would be helpful to know exactly what occurred at that time. In any event, this patient, who should have had heart murmurs, apparently never had them. Even though she was followed at frequent intervals thereafter by any number of competent observers no murmurs were ever heard. Other details I should like to know are whether she was cyanotic at birth and the state of her mother's health during the pregnancy. In any event, at some time after beginning school at about the age of seven, she began to be cyanotic, to tire easily and to be unable to keep up with the other children — an indication that she was encroaching upon a limited cardiac reserve.

At the age of ten she began to have syncope. Syncope occurs as a manifestation of heart disease most often in Adams–Stokes disease, in complete heart block with fluctuations of rhythm, occasionally in paroxysmal arrhythmias with unusually rapid rates, in coronary-artery disease, rarely with angina,

FIGURE 2.

in aortic stenosis and in cor pulmonale. It especially occurs in heart disease secondary to lung disease; I can recall having several such patients whose primary complaint was fainting. I might add that no one knows why these people faint. Some of these patients also have angina pectoris or something much like angina. I have observed a man with Eisenmenger's complex who had fainting spells. In this particular case there was some question about epilepsy as well. When we saw the patient during such an attack he had ventricular tachycardia. Some patients with congenital heart disease are prone to paroxysmal arrhythmias, which in some cases is sufficient to produce syncope. It is interesting that during the terminal episode, which was apparently not too unlike the previous attacks, the patient had a pulse of 70. Whether the pulse was regular or not is not mentioned. The assumption is that it was.

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It is interesting that she had the attacks commonly with overeffort and could produce them regularly by walking up two flights of stairs. This too is characteristic of the fainting spells that occur with cor pulmonale.

I do not know how to fit in the throbbing headaches and do not know that they contribute anything.

The physical examination was very interesting. The patient was cyanotic, and had clubbing of the fingers. I wish we had been informed whether there was any discrepancy between the degree of the cyanosis and the degree of the clubbing. The greatest obstacle in arriving at a diagnosis in this case is the absence of thrills or murmurs. There were two heart sounds or at least a split second sound, which was loud and could be felt over the pulmonary area. This suggests that the pressure in the pulmonary artery was very high. The two heart sounds in systole in the pulmonic area are troublesome. Nothing in the pulmonary valve produces first sounds; they are produced by the mitral and tricuspid valves and should be heard best over the lower part of the heart. I should have expected, with two first sounds and two second sounds, a bundle-branch block on the electrocardiogram; that was not observed, but the patient did have the pattern of hypertrophy of the right ventricle.

Dr. William R. Owen: I think everybody agreed that she had cyanosis and clubbing. In the pulmonary area I heard a systolic murmur, and a loud palpable pulmonic second sound was apparent. I estimated the murmur as only Grade 1 or 2.

Dr. Allan M. Butler: I wonder if Dr. Nadas can tell us more about these murmurs.

Dr. Alexander Nadas: I think we called the systolic murmur Grade 2 in the pulmonary area. I do not recall the other sound heard in systole. The cyanosis and clubbing were both definite; I should call them ++ or +++.

Dr. Howard B. Sprague: Such an additional systolic sound might be related to the pulmonic and aortic valves since in opening they contribute to the first heart sound. Dr. Nadas has suggested, in valvular pulmonic stenosis, that the accentuation of the third component of the first heart sound is due to the "slapping-sail" effect of the pulmonic valve as it attempts to open.

Dr. Littmann: May I see the x-ray films, Dr. Gibbons?

Dr. John F. Gibbons: There is a definite enlargement of the pulmonary-artery segment of the cardiac silhouette and also, in the lateral view, enlargement arteriorly of the right ventricle. The other cardiac chambers, as far as I can tell from these films, are all of normal size. The lung fields are normally vascularized. There is no abnormal indentation on the barium-filled esophagus.

Dr. Littmann: The vascular channels in the lungs are not too large or too small?

Dr. Gibbons: If anything, they are sparse, but I think one can see good-sized vascular channels throughout the cardiac silhouette.

Dr. Littmann: Two features of the circulation times are fascinating: the amount of Decholin used, and the times themselves — seven and eight seconds. This girl, who was apparently of normal size for her age, was practically an adult. It has been my experience that in people with normal hearts an end point cannot be obtained with 1 cc. of Decholin; it takes 2.5 cc. to 3 cc. In general the amount of Decholin required to determine a circulation time varies with the speed of the circulation time. People who are in congestive heart failure and in whom a long circulation time is anticipated may require 5 cc. Only in patients with unusually rapidly circulations can one expect to obtain an end point with 1 cc. I asked Dr. Myers what the normal circulation time was for a fifteen-year-old girl. He believed that it should not be much different from an adult's — perhaps as short as twelve or as long as twenty seconds. If she had been nervous, excited or febrile, the circulation time might have gone down to eleven or ten seconds, but it surely should not have decreased to seven seconds. Was the circulation time of seven seconds, therefore, a manifestation of an abnormal shunt from right to left, or could a circulation time that brief occur in conditions with high output and rapid circulation such as cor pulmonale? I have not yet settled that question in my mind. Certainly, if there was an abnormal shunt from right to left all the Decholin did not cross the shunt into the systemic circulation. For the sake of argument, let us assume that half of it passed through the shunt. In that case I am asked to believe that an end point was obtained with 0.5 cc. of Decholin. This I find difficult to accept. It would imply that there was a defect high in the ventricular septum and that the right ventricle squirted its contents almost directly into the left ventricle.

The patient became restless and died in a fashion that is fairly characteristic of some patients with pulmonary heart disease. I have observed 2 such cases, and I have heard of others. The patients died suddenly, unexpectedly, sometimes after a meal and commonly without any apparent cause; at autopsy there was no obvious reason for death — at least there was no evidence of a cerebral or cardiac accident.

I have to decide whether this was a case of congenital heart disease, with cyanosis, or of pulmonary vascular disease or possibly a combination of the two. Most cases of congenital heart disease with cyanosis have this throughout life with the notable exception of those with Eisenmenger's complex. In this condition even though there is a shunt, or the possibility of a shunt, with an overriding aorta that receives blood from both ventricles, the amount normally entering the aorta from the right ventricle is insufficient to cause cyanosis, at least in the early

years of life, but as the child grows older, vascular changes occur in the lungs. Increasing pressure in the pulmonary tree forces larger and larger quantities of blood from the right ventricle to be shunted into the systemic circuit, resulting in cyanosis. Therefore, Eisenmenger's complex is a definite possibility in a girl who manifested cyanosis at some time before her tenth birthday. Yet there are several details that militate against this diagnosis. In the first place there was little or no murmur. The few patients that I have seen — and I can number them on the fingers of one hand — all had systolic murmurs of considerable intensity and frequently diastolic murmurs, which arose from the aortic or pulmonary valve. Moreover, strain appears on both ventricles so that there is commonly no evidence of right-ventricle hypertrophy by electrocardiogram. There may be normal axis deviation and, in some cases, hypertrophy of the left ventricle. The presence of right-ventricle hypertrophy makes this diagnosis unacceptable, at least at the moment.

Another lesion that could conceivably account for the findings is the tetralogy of Fallot in which there are sometimes few murmurs but with which there should be cyanosis from birth and evidence of inadequate physical development. This girl was well developed for her age. With isolated pulmonary stenosis there may be a large pulmonary artery, but here too I should anticipate not only a loud murmur but other manifestations. A single ventricle could conceivably have produced this picture, but I find it hard to accept. In view of the history of rheumatism, I suppose I ought to consider the possibility of mitral stenosis, which can cause cyanosis, but I am not sure it ever does to this degree. Though I have less faith in the presence or the absence of murmurs than I once had, I still find it difficult to accept mitral stenosis as occurring in a heart without any apical diastolic murmur.

The diagnosis of primary pulmonary vascular disease is one that agrees with many aspects of this case. This is a condition that, for the most part, has an unknown origin, occurs at any age, including infancy, and in either sex — in the few cases that I have looked up, it was predominantly in the female. It is thought by some to be of congenital and by a few investigators to be of rheumatic origin, but for the most part nobody quite knows the etiology of the sclerotic changes that are seen in all coats of the small and medium vessels of the pulmonary tree. In some cases there is evidence of thrombosis of the smaller vessels with subsequent organization. This I suppose is the same as Ayerza's disease or the so-called black cardiac disease. Patients with this condition show an inexorable progress, with a fatal termination in a few months to as long as fifteen years. These people have weakness, vertigo, shortness of breath, cyanosis and clubbing; they may have anginal pains and fainting spells and may die suddenly. The description fits this particular case. But I wish that the circulation time had not been quite so brief. In the articles I looked up no mention was made of the circulation time except in one by Taquini et al.[1] A few years ago they studied some 10 cases in which the circulation time was actually slow. However, all the patients were older and were in heart failure at the time. The slow circulation time may have been due in part to the heart failure and in part to the increased viscosity of the blood resulting from its high cellular and protein content.

I am left, therefore, with these two possibilities. Still another that might be considered a straddle between them is primary pulmonary vascular disease existing simultaneously with a patent foramen ovale. In Eisenmenger's complex, the same situation exists; there is a congenital defect followed as in this case by pulmonary vascular disease. However, I shall say that this girl had primary vascular arteriosclerosis of the lungs and no congenital heart disease; my second possibility is Eisenmenger's complex.

DR. BUTLER: Dr. Nadas was the visiting physician when this child was admitted to the Children's Service. As his period of service ended a day or two after her admission he, for the purpose of this conference, may have the advantage of not knowing the autopsy findings.

DR. NADAS: When we talked about this patient on rounds I think I came to about the same conclusion that Dr. Littmann has reached — that is, primary pulmonary hypertension based primarily on increased pulmonary arteriolar resistance. We have seen children with identical clinical, radiologic and electrocardiographic pictures who turned out to have that condition. They also had the syndrome of weakness and syncope. I should not be surprised if one would have to straddle the fence and assume the presence of two conditions, the second being a communication between the two sides of the circulation, to explain as long lasting and as deep a cyanosis as this girl had. I should still call it primary pulmonary hypertension, however, and assume that the defect between the two sides probably did not have a causal relation to the increasing pulmonary arteriolar resistance. We have seen a series of children with ventricular defects whom we have had the opportunity of following from infancy; their lung fields always looked ischemic. They did not go through a phase of increased flow that caused pulmonary arteriolar disease and thus resulted in the picture of ischemic lung fields; if the lungs were ischemic at ten or fifteen years of age, they were also ischemic at ten months. I have seen this picture in patients who we know have defects of the ventricular septum; hence I would bring in the diagnosis that there was a primary pulmonary hypertension, which does not necessarily exclude the presence of a defect between the two sides of the heart, but I do not know that the two were in causal relation.

DR. GORDON S. MYERS: I might say that in this hospital we have seen patients with pulmonary vascular disease and a defect of either the auricular or the ventricular septum or a patent ductus arteriosus with little or no murmur.

DR. H. L. HEYL: How long before death was the Decholin given?

A PHYSICIAN: Actually, the patient was dead about twenty minutes after the Decholin was given, but she was not pronounced dead until forty-five minutes later; we tried for ten minutes to revive her.

A PHYSICIAN: Do you think the Decholin was in any way responsible for the death?

DR. LITTMANN: Literally, millions of tests are performed with Decholin, and nothing ever seems to happen. There was some warning about the use of ether in people who are assumed to have a right-to-left shunt; apparently deaths have occurred under that particular circumstance. I think in this case the use of Decholin per se had little to do with the outcome. It should be remembered that the patient had syncopal attacks with emotional trauma; perhaps the procedure itself was enough of a nervous shock to precipitate an attack.

DR. BUTLER: The physicians on the service were apprehensive about carrying out procedures necessary to establish the diagnosis; they believed, however, that the diagnosis could not be made without so doing and selected as the first procedure one they assumed to be the least fraught with danger.

DR. LITTMANN: Whatever the diagnosis turns out to have been this was probably not a case in which surgery would have been expected to be of benefit.

DR. NADAS: Yes; at the same time we are justified in trying to find out all we can about a girl whose cardiac reserve was very limited and who could have had a lesion such as pulmonary stenosis and a patent foramen ovale, which, however, did not seem likely. At the time, in view of the severity of the condition, we believed that diagnostic procedures were justified.

DR. JOHN T. QUINBY: Did you ever see a pulmonary arteriovenous shunt that was large enough to cause this amount of cyanosis but that was not visible in the x-ray films of the lung?

DR. LITTMANN: To cause this amount of cyanosis I should think it would have to be visible.

CLINICAL DIAGNOSES

Congenital cyanotic heart disease.
Pulmonary endarteritis, with pulmonary hypertension.

DR. DAVID LITTMANN'S DIAGNOSIS

Primary vascular arteriosclerosis of lungs.
?Eisenmenger's complex.

ANATOMICAL DIAGNOSES

Congenital heart disease: aortic-pulmonary-artery septal defect.
Pulmonary vascular disease.

PATHOLOGICAL DISCUSSION

DR. ROBERT H. FENNELL, JR.: We found at autopsy that the heart was not enlarged. It weighed 270 gm., not excessive for a patient of that size, but the right ventricle was greatly dilated and hypertrophied. The wall was 14 mm. thick, the same as the left ventricle, and in the volume of the cavity and appearance of the papillary muscles, the two ventricles were similar. The valves were all normal. Nothing suggestive of rheumatic fever was found in the valves or myocardium. The foramen ovale was closed. The origin and distribution of the coronary arteries were normal. The only abnormality of the

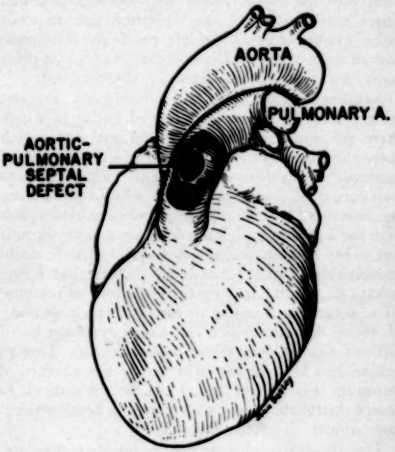

FIGURE 3.

heart or great vessels was a defect in the septum between the aorta and pulmonary artery (Fig. 3). This was a rounded opening, 1.2 cm. in diameter, and was located 1 cm. above the upper edge of the aortic cusps. We could dissect between the aorta and pulmonary artery below the communication to make a space 1 cm. long, a distance above the right coronary artery that was probably sufficient for the surgeon to have attacked this lesion. The edge of the defect was smooth, and the walls of the two vessels seemed to be fused. Beyond the defect the aorta and pulmonary artery branched normally. There was mild atherosclerosis in the main pulmonary artery. The ductus arteriosus was closed.

Embryologically, such a defect represents incomplete partitioning of the truncus arteriosus. In the 5-mm. embryo two ridges grow into the lumen

of the large vessel that extends cephalad from the heart, and these two ridges meet to separate the vessel into pulmonary artery and aorta. Presumably, in one area the two ridges did not meet in this patient, and so a communication remained. Collett and Edwards[3] consider this a variation of a persistent truncus arteriosus and classify it as Type 5.

This is an uncommon anomaly as judged by the few available cases, only about 25 having been reported up till several years ago. That number has been increased by recent reports of cases that were diagnosed clinically either by aortography or by catheterization or were found accidentally at the time that an operation was being performed with the intent of ligating a patent ductus arteriosus. Gasul and his co-workers[3] have diagnosed 1 case by retrograde aortography, and Dexter,[4] at the Peter Bent Brigham Hospital, found such a case by accidentally placing a catheter through the opening between the aorta and pulmonary artery. Adams et al.[6] also report 5 cases of this type of anomaly recognized by catheterization studies. Of the several cases that have been recognized at operation after a misdiagnosis of patent ductus arteriosus 1 is reported from this hospital[5] and 4 cases are reported by Gibson and his associates.[7] Gross[8] has operated on a patient who was thought clinically to have a patent ductus arteriosus; at operation this type of defect was found and successfully repaired. Scott and Sabiston[9] have also performed such an operation with a successful result. It is therefore not merely of academic interest to diagnose this condition.

Most of the cases have been similar to this one. The defect is usually in the first several centimeters of the aorta, and the defect has varied from 0.5 to 3.0 cm. in diameter. There are no consistently associated anomalies, and when other anomalies are present they are usually of little significance. The clinical picture is not distinctive, and, as indicated above, most of these cases have been diagnosed as patent ductus arteriosus.

An acquired communication may simulate this condition, and some of the cases reported seem to have been of this nature. Shepherd's[10] and Moorhead's[11] cases are probably examples of this. There is a possibility that a patent ductus arteriosus will be mistaken for aortic-pulmonary septal defect, and Lutembacher's[12] case seems to have been an example of such a misinterpretation.

Of the remainder of the autopsy study, only the lungs were significant. They were light and fluffy. The pulmonary arteries were conspicuous, even toward the periphery of the lung. The bronchial arteries when injected were slightly more prominent than usual, but there was no striking change in them. Microscopical study of the lungs revealed changes in the vessels that are somewhat puzzling. There was fibrous intimal thickening of the arteries and arterioles, and a few of the vessels contained organized thrombi or emboli because there were multiple lumens lined by endothelium and separated by loose connective tissue (Fig. 4). Many of the small arteries were completely occluded by loose connective tissue. In the walls of many of these one could find multinucleated giant cells in what was apparently the lumen and adjacent to the internal elastic lamina but also farther out in the wall (Fig. 5). In a few places evidence of phagocytosis of the elastic tissue by the giant cell was found — a picture that one sees typically in the so-called giant-cell or temporal arteritis. Also, adjacent to some of these giant cells were small flecks of calcium. There was no evidence of necrosis in the vessel wall and no evidence of an acute reaction. The media of the arteries and arterioles did not seem to be thickened.

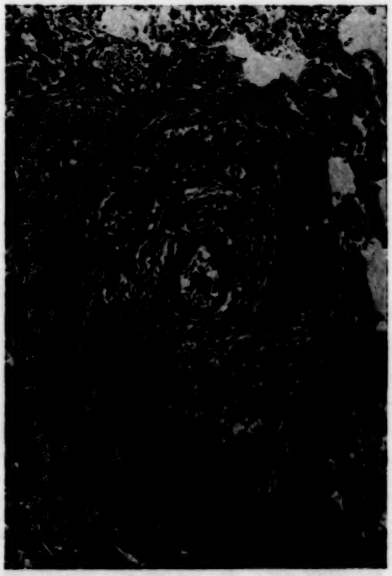

FIGURE 4. *Recanalized Thrombus, with Multiple Lumens in a Small Artery (300 Microns).*

We know from experimental observation and from what Castleman and Bland[13] have seen in human patients that changes such as this can result from emboli. Barnard,[14] in England, injected autogenous fibrin thrombi and described acute arteritis and also described some giant-cell reaction in the walls where the fibrin was being deposited. The

intimal thickening may be due to organized emboli or thrombi such as Muirhead and Montgomery[15] produced experimentally in animals. We demonstrated no source for emboli however, and I do not know that we should particularly suspect that. Perhaps they were thrombi. The fibrous intimal thickening resembles what has been seen here in a study by Thomas and others.[16] It is also similar in some respects to the vascular changes that one sees in mitral stenosis.

FIGURE 5. *Small Artery (300 Microns) with Giant Cells Adjacent to the Internal Elastic Lamina and Deep in the Media. The lumen is filled with loose connective tissue and scattered inflammatory cells.*

In summary, this patient had a congenital heart lesion but had in addition pulmonary vascular changes, which I am quite sure were secondary to the congenital heart lesion, but I have no absolute proof of that. The incidence of thrombosis and embolism is so common with heart disease that I believe the association is more than coincidental. Some of the intimal proliferation was undoubtedly due to the pulmonary hypertension, but I do not believe that that is the whole story.

DR. SPRAGUE: Was the head examined?

DR. FENNELL: It was normal.

DR. ALLAN FRIEDLICH: Are some of the changes in the pulmonary vessels similar to those described by Rich[17] in patients with the tetralogy of Fallot? These patients also have decreased pulmonary blood flow and increased blood viscosity that may lead to thrombus formation.

DR. FENNELL: They do resemble them. I am not sure where they fit with this picture, though, because here the flow is greater, not less, than normal.

DR. BUTLER: At first thought one wonders why the x-ray films did not show increased blood flow in the pulmonary vessels. I suppose, however, that pulmonary vascular disease prevents increased blood flow through the vascular bed.

DR. FENNELL: I think there must have been quite a marked embarrassment of flow through them. We injected the bronchial artery and found that the pulmonary vessels were prominent but not markedly so.

DR. SPRAGUE: I think the point that Dr. Nadas brought up is very important. He says that, in successive x-ray films taken over a period, he at no time saw the lungs full of blood. In the usual case in the adult, which we may see in only the fully developed state, we usually do not have the advantage of a previous knowledge of what the lungs looked like on x-ray examination. Here, however, there is definite evidence that the pulmonary pattern was always that of decreased, rather than increased, vascularity; in other words, the vascular changes were not secondary to mechanisms of excessive blood flow.

DR. NADAS: There is one other point. It seems inconceivable to me that a girl with a large enough left-to-right shunt to have resulted in these changes should have grown up to have a normal-sized heart at the age of fifteen. All those in whom this condition develops on the basis of a pre-existing large pulmonary flow have large hearts.

DR. MYERS: Furthermore, these changes may occur very early in life. We had a recent patient with patent foramen ovale and marked pulmonary vascular disease whose symptoms began shortly after birth and who died at two and a half years of age.

DR. NADAS: That case was similar to the one under discussion. I have seen one at autopsy at the

Floating Hospital with pulmonary vascular changes alone and no septal defect.

DR. FENNELL: I was impressed with its resemblance to the changes seen in the vessels of other patients with congenital anomalies who have associated pulmonary hypertension.

DR. SPRAGUE: And they are not confined to vessels of one caliber like the ones described by Castleman and Bland?[18]

DR. FENNELL: The most marked findings were in the small arteries. There was some thickening in the small arteries and arterioles, but the changes that I think were organized thrombi, or emboli were primarily in the small arteries.

DR. OWEN: Some believed that the Decholin was responsible for the patient's death. I wonder if Dr. Fennell knows of any such reactions.

DR. FENNELL: I am afraid I cannot explain it very well.

DR. MYERS: I do not think it is possible to be at all certain of the mechanism of death, but one possibility is that there was eventually a sharp decrease in systemic resistance, which increased the right-to-left shunt at the base of the aorta and therefore flooded the coronary and cerebral circulation with unoxygenated blood.

DR. EDWARD F. BLAND: The reason for this is that the systemic blood pressure had gone up.

DR. MYERS: That was the earliest effect, but the blood pressure then fell again.

DR. LITTMANN: I had a patient with a different background who died recently. That was a man who had similar lung disease resulting from numerous minute emboli, essentially the Bland–Castleman condition, and who during a meal, died between mouthfuls. There was no other precipitating factor. That seems to be the usual manner of death of people with gross pulmonary hypertension.

REFERENCES

1. Taquini, A. C., Fasciolo, J. C., Suarez, J. R. E., and Chiodi, H. Circulatory adaptations in Ayerza's syndrome — black cardiacs. *Am. Heart J.* 34:50-64, 1947.
2. Collett, R. W., and Edwards, J. E. Persistent truncus arteriosus: classification according to anatomic types. *S. Clin. North America* 29:1245-1270, 1949.
3. Gasul, B. M., Fell, E. H., and Casas, R. Diagnosis of aortic septal defect by retrograde aortography. *Circulation* 4:251-254, 1951.
4. Dexter, L. Cardiac catheterization. *Modern Medicine*, February 15, 1949. P. 96.
5. Adams, F. H., Diehl, A., Jorgens, J., and Veasy, L. G. Right heart catheterization in patent ductus arteriosus and aortic-pulmonary septal defect. *J. Pediat.* 40:49-59, 1952.
6. Myers, G. S., Scannell, J. G., Wyman, S. M., Dimond, E. G., and Hurst, J. W. Atypical patent ductus arteriosus with absence of usual aortic-pulmonary pressure gradient and of characteristic murmur. *Am. Heart J.* 41:819-833, 1951.
7. Gibson, S., Potts, W. J., and Langewisch, W. H. Aortic-pulmonary communication due to localized congenital defect of aortic septum. *Pediatrics* 6:357-360, 1950.
8. Gross, R. E. Surgical closure of aortic septal defect. *Circulation* 5: 858-863, 1952.
9. Scott, H. W., Jr., and Sabiston, D. C. Surgical treatment for aortico-pulmonary fistula: experimental and clinical aspects. Presented at the annual meeting of the American Association for Thoracic Surgery, Dallas, Texas, May 10, 1952. (Cited by Downing, D. E., Bailey, C. P., Maniglia, R., and Goldberg, H. Defect of aortic septum. *Am. Heart J.* 45:305-314, 1953.)
10. Shepherd, S. G., Park, F. R., and Kitchell, J. R. Case of aorto-pulmonic communication incident to congenital aortic septal defect: discussion of embryologic changes involved. *Am. Heart J.* 27:733-738, 1944.
11. Moorhead, T. G., and Smith, E. C. Congenital cardiac anomaly: abnormal opening between aorta and pulmonary artery. *Irish J. M. Sc.* 8:345-549, 1923.
12. Lutembacher, R. Communication entre l'aorte et l'artère pulmonaire. *Presse méd.* 53:577, 1945.
13. Castleman, B., and Bland, E. F. Organized emboli of tertiary pulmonary arteries: unusual cause of cor pulmonale. *Arch. Path.* 43:581-589, 1947.
14. Barnard, P. J. Experimental fibrin thrombo-embolism of lungs. *J. Path. & Bact.* 65:129-136, 1953.
15. Muirhead, E. E., and Montgomery, P. O'B. Thromboembolic pulmonary arteritis and vascular sclerosis. *Arch. Path.* 52:505-517, 1951.
16. Thomas, W. A., Owen, W., Castleman, B., and Bland, E. F. Unpublished data.
17. Rich, A. R. Hitherto unrecognized tendency to development of widespread pulmonary vascular obstruction in patients with congenital pulmonary sclerosis (tetralogy of Fallot). *Bull. Johns Hopkins Hosp.* 82:389-401, 1948.

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"GATHER YE ROSEBUDS"

THE progress report on the effect of aging of population on general health problems, concluded elsewhere in this issue of the *Journal*, is an admirable exposition of a problem that, never new, has grown in importance in recent years. The fact of an increase in life expectancy with a spectacular decline in mortality rates is well known; Monroe's paper deals with the ways in which the complexities of advancing age are to be met rather than with the factors that have been responsible for the aging population.

Life expectancy, as a matter of fact, presents to the uninitiated a somewhat curious biostatistical anomaly, for whereas the person of sixty had in 1940 an expectancy of 16.57 additional years ahead, the presumably somewhat enfeebled centenarian had himself a very respectable expectancy of over two years; his chances of living to 102, despite his frailties, were infinitely greater than those of the most robust youth.

It is to be noted, however, with all this improved expectancy, that there has been no remarkable increase in the numbers of persons attaining great age, nor in the years that they attain — such records would be hard to beat if certain Biblical references are to be accepted. The increase to be reckoned with is in the number of so-called aging persons, constituting a rapidly expanding minority group that may be said to have its anlage in middle life, when the economic and social hazards of growing older begin.

Monroe pays due respect to the emotional hazards of reaching one's fiftieth and sixtieth birthdays, when the life-expectancy tables may be invoked in the cause of mental therapy. These tables are fortunately unexpectedly generous, giving substance to the pleasant reflection that there may be life in the old dog yet; a glance at them may surprise the doctor and encourage the patient to settle down "to behave as a permanent resident and not as a spectator on call."

There remain the social, economic and medical problems to try to settle, with certain principles of practice to be observed that apply particularly to the aged and the old, but that nevertheless treat them as going concerns or rather, as Monroe prefers to phrase it, continuing, not going organisms. Necessary and even preventive surgery should be performed as indicated. The milder mental disorders of the deteriorating oldster should be discounted as far as possible, with the cheering thought in mind that relatively few patients show clinical evidence of cerebral sclerosis and fewer still have definite personality changes as a result of this process.

Housing and protection from fire hazards must be considered, suitable occupation needs to be provided, and it must be remembered that loneliness and loss of appetite often go together. Drugs should be used sparingly, especially the barbiturates, which do not control emotional tension or reduce blood pressure as well as they are supposed to, and amphetamine, which is no improvement over coffee

and tea in elevating the mood. Symptomatic treatment is no more rational in the old than in the young.

Some regret but also some good advice can be found in the words of the octogenarian, Herrick, to be applied at any age, but requiring some paraphrasing for these modern days of more young people growing older and more old people staying younger:

> Gather ye rosebuds while ye may,
> Old Time is still a-flying,
> But this same flower that smiles today
> Will be a long time dying.

CARBOMYCIN ("MAGNAMYCIN")

A TREMENDOUS amount of effort and large sums of money are being expended in many laboratories in attempts to discover new, active and useful antimicrobial agents. The intensive research and screening programs under way were designed particularly to discover substances active against infections that are not now adequately controlled by the agents currently available, or have equal or greater activity but lower toxicity or less sensitizing properties in human beings. For the manufacturers or commercial sponsors of a new and useful antibiotic, this means considerable prestige and, if the agent is active against a wide spectrum of infections or against infections that are particularly prevalent, it also means not only adequate compensation for the expenses of carrying out the research programs but also well deserved and sizable financial rewards. The intense desire on the part of manufacturers to explore the potentialities of any new and promising agent that their research workers turn up is laudable, and their attempts to exploit, as much as possible, those which prove to be useful can readily be understood and appreciated.

One of the newest of the antimicrobial agents to receive a clinical trial is carbomycin; data presented by a number of workers in the Research Laboratories of Charles Pfizer and Company, where it was discovered and developed under the trade name of "Magnamycin," indicated that it had most of the properties desired of a useful antibiotic and, therefore, was worthy of clinical exploration. The spectrum of its antibacterial action embraced primarily the same organisms as penicillin, but it included many strains of gram-positive cocci, particularly staphylococci and enterococci, that were moderately or markedly resistant to that agent and to some of the other commercially available antibiotics. It was also said to be active against rickettsias and some large viruses. In rabbits it appeared to be fairly well absorbed from oral administration, and parenteral injection seemed feasible. Its acute and chronic toxicity in laboratory animals was found to be slight.

Three reports of the clinical use of carbomycin in various infections have now been published in this journal, including one in this issue, which also contains a summary of the published information thus far made available. The first of these reports[1] was a highly encouraging one on the treatment of 15 patients with genitourinary infections due to carbomycin-sensitive organisms; favorable results were obtained in 13 of these patients although the majority had previously failed to respond to sulfonamides or other antibiotics. However, it was noted that these favorable responses occurred in spite of the fact that concentrations of carbomycin in the blood and urine of these patients were insignificant. These findings were interpreted as indicating that the levels of carbomycin found in blood and urine are of questionable value as indications of response to the drug. However, they are also subject to the interpretation that the recovery of the patients may not have been related to the treatment with carbomycin. Only 7 other patients with urinary-tract infections due to susceptible organisms are included in the other two reports, but only 2 of them showed a favorable response; the failure to achieve significant concentrations in blood or urine was also confirmed in these reports.

Except for a single encouraging report, the overall results of the clinical trials thus far described have not been particularly favorable; they include, in addition to the studies already mentioned, an earlier one[2] on 5 patients treated with carbomycin for staphylococcal infections and a more recent one[3] on its use in 8 patients with pneumococcal pneumonia. More than half the patients with pneumonia included in all the reports appeared to improve under treatment, but at present this cannot be considered as a notable achievement and, indeed, may not be significantly more than is to be expected

in patients without antimicrobial therapy. Particularly discouraging has been the failure to eliminate pneumococci from the sputum and even from the blood of an appreciable number of patients during treatment with oral doses that approach the maximum that can be tolerated. Persistence of pneumococci in the blood in uncomplicated cases of pneumonia has not been observed during the administration of therapeutic doses of any of the active agents that have been recommended for the treatment of pneumonia, beginning with the introduction of sulfapyridine and including the well absorbed sulfonamides that followed, and then penicillin and each of the three broad-spectrum antibiotics. It has, however, been reported recently during treatment with erythromycin.[3]

The hope that another active agent would be available for the treatment of some of the serious infections with staphylococci and with certain streptococci (other than those of Group A) that are resistant to penicillin and some of the other available antibiotics has not been fulfilled; unfortunately, carbomycin has failed to exert a favorable influence in the great majority of the patients with such infections that were included in the available reports. In addition, assays of blood and urine of patients under treatment have usually failed to yield concentrations of carbomycin sufficient to inhibit most of the strains of these organisms.

Carbomycin, therefore, cannot now be recommended for the treatment of bacterial infections and, at least according to two of the reports, it may be considered to be contraindicated in pneumococcal infections chiefly because it might deprive patients of the use of other agents, all of which are known to be highly active in these infections. However, carbomycin may find other fields of usefulness. Other antibiotics that for reasons of toxicity, absorptive properties or limited activity have not lived up to full expectations when applied clinically have nevertheless found some circumscribed areas of usefulness. Tyrothrycin, polymyxin, bacitracin, viomycin and neomycin are examples of such antibiotics; these have proved highly useful either in specific infections, as a second choice, or when used by special methods of application. It has been suggested that the effects reported from carbomycin against amebas, both in vitro and in 5 clinical cases of amebiasis, warrant further explorations of its usefulness against certain intestinal parasites.

It is to be hoped that the intensive efforts to discover new antimicrobial agents will continue despite the many disappointing experiences already encountered. Although there have been many predictions accompanying the release of the earlier antibiotics to the effect that infectious diseases have at last been conquered, large numbers of serious infections against which active agents are urgently needed still remain. Too many persons are still dying of such infections in spite of the intensive use of all the agents currently available.

References

1. Trafton, H. M., Lind, H. E., and Correia-Branco, M. Treatment of urinary-tract infections with new antibiotic — Magnamycin: preliminary report. *New Eng. J. Med.* 248:379, 1953.
2. Finn, J. J., Jr., and Kane, L. W. Magnamycin, new antibiotic (preliminary note). *Bull. New Eng. M. Center* 14:113-116, 1952.
3. Bunn, P. A. Use of Magnamycin and erythromycin in the treatment of pneumococcal pneumonia. *J. Clin. Investigation* 32:557, 1953.

KINGS COUNTY GOES ON RECORD

The Kings County Medical Society of Brooklyn, New York, at a meeting on June 30, strongly expressed its views on certain controversial points in medical relations. These views took shape in resolutions to the New York State Medical Society recommending four changes in the Society's *Code of Ethics*.

According to the first of these resolutions, as reported in the *New York Times* on July 2, no prepayment medical-care program that advertised for clients would be approved, and presumably the participation of physicians would be declared unethical. This puts on the line one of the grievances held by the independent practitioner against practically all prepayment medical-service plans — and it seems a legitimate one: that they can solicit business in a way that is denied to him.

The second resolution adopted in Kings County would restrict the treatment of patients by hospitals and other clinics to those who are "public charges" — not merely medically indigent but poor or needy in the usual sense of the word. This restriction, if and where it became operative, would remove certain organized competition to the independent practice of medicine and would have the effect of favoring the practitioner regardless of the best interests of

the patient. It might also affect the hospital-physician form of group practice, favored by many persons within as well as outside the profession as the most practical group arrangement that has so far been proposed.

The third resolution consists apparently of a blanket disapproval of the offering of services to patients by hospitals or clinics because of their interference with the patient's free choice of physician. This controversial issue, which has developed to the point of becoming a rallying cry, is difficult to evaluate with all its possible ramifications, and to find an unmistakably clear principle to which to cling. Free choice of physician within geographic and economic limits and the willingness of the chosen physician to comply should be preserved as a democratic institution.

It is obvious that this choice is denied to the indigent, to those who are voluntarily or involuntarily patients in many municipal, state, and federal hospitals, and to members of the armed forces. The patient voluntarily going to any medical-practice group surrenders at least temporarily certain privileges, such as his own choice of a consultant. It would seem that free choice of physician requires careful definition before it can be established as an absolute commandment.

The fourth resolution, which may or may not admit debate, except that all matters are — or should be — debatable, relates to the proration of fees between or among physicians if commensurate with the services rendered and if other conditions are met. It is possible that certain arrangements openly entered into and properly safeguarded might in certain cases give the family doctor a better deal, free from the clandestine and illicit atmosphere of direct fee splitting with all its ugly connotations.

The truth, recognized by those who seek it, is that the practice of medicine is changing and will change, and that in its evolution the interests of both patient and physician must be considered, but that the patient's must come first, that being the rock on which the doctor's creed is founded. Violent controversy between extreme viewpoints is destructive; reasonable debate and compromise will be productive of the best results in giving direction to the changes that are inevitable in all human relations.

MEDICAL LIBRARY NEARS THE TOP

The Greater Service Program of the Boston Medical Library, after only two months in operation, found the top in view on July 17. On that date over $205,000 of the $250,000 that had been established as the initial phase of the long-term campaign had been pledged and partly paid.

Of the special gifts committee of 150 members, 43 had completed their assignments by the mid-July date, and a total of 766 gifts amounting to $205,224 had been reported. The 413 cards still unreported will unquestionably put the program well over the top.

Certain figures from the present report are of interest. Thirteen per cent of the gifts received are above $500 and 54 per cent are above $150. Eighty-nine per cent of the prospects interviewed have contributed — a most unusual response. An appeal by mail to the physicians of the state produced $14,030.

The immediate needs of the Library, to be served by the present campaign, so near to fulfilment, are to erect the remaining stacks and install the necessary elevator in the stack wing, to complete the periodical room — still unfinished, although functioning for twenty-three years — and to make certain needed repairs required by the Boston Building Department. The funds necessary to finish the Periodical Room have already been contributed by his associates as a memorial to the late Dr. Frank H. Lahey, and opportunities are available for other memorial or named gifts.

Only a little effort will be required on the part of those who have not completed their assignments to put this remarkable campaign over the top and to demonstrate that intellectual as well as emotional appeals are heeded.

Medical Reporter. — *Pennsylvania bids fair to have as many medical journals as schools of medicine. The first number of a new Quarterly; with the above title, under the editorial management of five medical gentlemen, and published at West Chester, has a fine appearance.*

Boston M. and S. J. *August 24, 1853*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

BARTOL — Edward F. W. Bartol, M.D., of Lancaster, died on August 6. He was in his eightieth year.

Dr. Bartol received his degree from Harvard Medical School in 1900. He was formerly on the staff of the Clinton Hospital.

He is survived by his widow and a son.

CLYMER — George Clymer, M.D., of Boston and Longmeadow, died on August 4. He was in his seventy-first year.

Dr. Clymer received his degree from Harvard Medical School in 1911. He was on the staff of the Massachusetts General Hospital before his retirement. He was a fellow of the American Medical Association and a member of the New England Society of Psychiatry and Boston Society of Neurology and Psychiatry.

Dr. Clymer is survived by his widow, two sons, a daughter and eight grandchildren.

GARLAND — Frederick E. Garland, M.D., of Wellesley, died on August 3. He was in his seventy-ninth year.

Dr. Garland received his degree from Harvard Medical School in 1902. He was formerly surgeon-in-chief, Department of Oto-Laryngology, Massachusetts Eye and Ear Infirmary, and chief surgeon, Henry Heywood Memorial Hospital, Gardner. He was a member of the New England Oto-Laryngological Society, a fellow of the American Academy of Ophthalmology and Oto-Laryngology and of the American Medical Association.

Dr. Garland is survived by his widow, a daughter and a son.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

The September schedule of the Consultation Clinics for Crippled Children is as follows:

Orthopedic	Date	Clinic Consultant
Gardner	September 1	Carter R. Rowe, M.D.
Haverhill	September 2	William T. Green, M.D.
Greenfield	September 3	Charles L. Sturdevant, M.D.
Brockton	September 10	George W. Van Gorder, M.D.
Lowell	September 11	Albert H. Brewster, M.D.
Salem	September 14	Paul W. Hugenberger, M.D.
Lynn*	September 14	Daniel M. Killoran, M.D., and John J. Crowley, M.D.
Springfield	September 15	James D. Fisher, M.D.
Pittsfield	September 16	Edward J. Coughlin, Jr., M.D.
Worcester	September 18	John W. O'Meara, M.D.
Hyannis	September 24	Paul L. Norton, M.D.
Fall River	September 28	David S. Grice, M.D.

Rheumatic-Fever Clinics	Dates
North Reading	September 1, 8, 15, 22, 29
Fitchburg	September 2, 9, 16, 23, 30

Plastic Clinic	Held	Consultant
Eastern Massachusetts	Semi-monthly	Bradford Cannon, M.D.
Western Massachusetts	Monthly	Joseph M. Baker, M.D.

Physicians referring new patients to clinic should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

*This clinic serves Lynn, Lynnfield, Saugus, Nahant, Revere, Chelsea, Everett and Winthrop. Referrals should be made directly to the Lynn Hospital.

BOOK REVIEW

Lumbar Disc Lesions: Pathogenesis and treatment of low back pain and sciatica. By J. R. Armstrong, M.D., M.Ch., F.R.C.S. With a foreword by H. Osmond-Clarke, C.B.E., F.R.C.S. 8°, cloth, 288 pp., with 56 illustrations, 21 plates and 7 tables. Edinburgh: E. and S. Livingstone, Limited, 1952. $8.00.

The author believes that lesions in the lumbar intervertebral disks are the commonest cause of pain in the lower back and of sciatic pain. He reviews the early pathological and clinical studies that led to the establishment of herniation of the intervertebral disks as a clinical entity. Causes, symptoms, diagnosis and treatment are adequately but concisely discussed. Conservative treatment, rest in bed and traction or a spica are advocated in patients with acute symptoms. In subacute symptoms a plaster jacket is considered most effective. Patients with early lesions are usually the only ones who respond well to conservative treatment, which may require several months. The author believes that counterirritants, local injections and manipulation are of no real value. The indications for surgical treatment are given as failure of conservative treatment, cauda-equina pressure and persistence of root pressure. Spinal fusion is not advocated when the herniated disk is removed but when the lesion is associated with spondylolisthesis, associated with marked arthritic changes or when severe incapacitating symptoms remain.

This is an excellent and concise summary of knowledge of herniated disks. The illustrations are good. The book is well written, with excellent references. It is the best exposition to date on this subject written by a surgeon of wide experience.

J. G. KUHNS, M.D.

NOTICES

ANNOUNCEMENTS

Dr. Richard N. Abbott announces the removal of his office to 14 West Central Street, Natick, for the practice of pediatrics.

Dr. Edward J. Healey announces the opening of an office at 270 Commonwealth Avenue, Boston, for the practice of radiology.

Dr. John W. Keller announces the opening of an office at 330 Dartmouth Street, Boston, for the practice of internal medicine.

SOUTH END MEDICAL CLUB

The next meeting of the South End Medical Club will be held Tuesday, September 15, at noon, at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston. Dr. Varaztad H. Kazanjian, professor emeritus of plastic surgery, Harvard University School of Dental Medicine, and honorary surgeon, Massachusetts General Hospital, will speak on "The Surgical Treatment of Selected Cutaneous Lesions."

All physicians are cordially invited to attend.

LIFE INSURANCE MEDICAL RESEARCH FUND FELLOWSHIPS AND GRANTS

Applications for awards available July 1, 1954, will be received by the Life Insurance Medical Research Fund as follows:

(1) Postdoctoral research fellowships, until October 31, 1953. Preference is given to those who wish to work on cardiovascular function and disease or related fundamental problems. Stipends vary from $3300 to $4500.

(2) Grants to institutions in aid of research on cardiovascular problems, until November 15, 1953. Support is available for physiological, biochemical, and other basic work broadly related to cardiovascular problems as well as for clinical research in this field.

Further information and application forms may be obtained from the Scientific Director, Life Insurance Medical Research Fund, 345 East 46th Street, New York 17, New York.

(*Notices concluded on page xvii*)